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(54) **COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF KLF-1 AND BCL11A GENES**

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35/28

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to double-stranded ribonucleic acid (dsRNA) compositions targeting the KLF1 gene and the BCL11A gene, and methods of using such dsRNA compositions to inhibit expression of KLF1 and BCL11A, respectively.

**44 Claims, 22 Drawing Sheets**

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FIG. 1

1 tcagagttca cgaggcagcc gaggaagagg aggetttagg cccaggggtgg gcaccagcca  
61 gccatggcca cagccgagac cgccttgccc tccatcagca cactgaccgc cctgggcccc  
121 ttcccgga caacagatga ctccctcaag tgggtggcgt ccgaagaggc gcaggacatg  
181 ggcccggtc ctctgaccc cagcgagccg cccctccacg tgaagtctga ggaccagccc  
241 ggggaggaag aggacgatga gaggggcgcg gacgccacct gggacctgga tctcctcctc  
301 accaacttct cgggcccggg gcccggtggc gcgcccaga cctgcgctct ggcgcccage  
361 gaggcctccg gggcgcaata tccgccgcg cccgagactc tgggcgcata tgctggcggc  
421 ccggggctgg tggctgggct tttgggttcg gaggatcact cgggttggtt gcgcctgccc  
481 ctgcgagccc gggtcccga cgccttcgtg ggcccagccc tggctccagc cccggccccc  
541 gagcccaagg cgctggcgt gcaaccggtg taccgggggc cggcgcccg ctccctcggtt  
601 ggctacttcc cgcggaccgg gctttcagtg cctgcggcgt cggcgccccc ctacgggcta  
661 ctgtccgggt accccgcgat gtaccggcg cctcagtacc aagggcactt ccagctcttc  
721 cgcgggctcc agggaccgc gcccggtccc gccacgtccc cctccttctt gagggtgtttg  
781 ggaccgggga cgggtgggcac tggactcggg gggactgcag aggatccagg tgtgatagcc  
841 gagaccgcgc catccaagcg aggcgcagct tcgtgggcgc gcaagaggca ggcagcgcac  
901 acgtgcgcgc acccggttg cggcaagagc tacaccaaga gctccacct gaaggcgcac  
961 ctgcgcacgc acacagggga gaagccatac gctgcacgt gggaaggctg cggtgggaga  
1021 ttgcgcgct cggacgagct gaccgcgcc taccggaaac acacggggca gcgccccttc  
1081 cgctgccagc tctgccacg tgctttttcg cgctctgacc acctggcctt gcacatgaag  
1141 cgccaccttt gagccctgcc ctggcacttg gactctccta gtgactggg atgggacaag  
1201 aagcctgttt ggtggtctct tcacacggac gcgcgtgaca caatgctgg tggttttccc  
1261 acgaatggac cctctcctgg actcgcgttc ccaaagatcc acccaaatat caaacacgga  
1321 cccatagaca gccctggggg agcctcttac ggaaaatccg acaagccttc agccacaggg  
1381 agccacacag agatgtccaa actgtcgtgc aaaccagtg agacagaccg ccaaataaac  
1441 ggactcagtg gacactcaga ccagctccca gatggccctg gacagcagga gaggggtgtg  
1501 gatgaggctt cccagagacc ctgggtctag aaagcggtc ctgaaggctt cttattgtgg  
1561 ctgatattaa ctgtcaatgg ttatgggtcc tataaaaatg cccctcccag ataaa

(SEQ ID NO:1)

**FIG 2.**

1 gtgggcagac aggagccctc caagaaactt tcctagcctc atagcccatg aggcagaaga  
61 gagagaggag gcctgaggtc caggggtggac accagccagc catggcctca gctgagactg  
121 tcttaccctc catcagtaca ctcaccaccc tgggacagtt cctggacacc caggaggact  
181 tcctcaagtg gtggcggtct gaggagacgc aggatttggg gccggggccc ccgaatccca  
241 cggggccgtc ccatcacgtg agtctgaaat cggaggaccc ttccggagag gacgatgaga  
301 gggacgtgac ctgtgcgtgg gaccgcgata ttttccttac aaactttcca gggtccgagt  
361 ctcccggcac ttcccggacc tgtgccctgg cgcccagcgt ggggccagtg gcacagttcg  
421 agccgcctga gtctctgggc gcctatgcgg gtggcccagg gttggtgact gggcctttgg  
481 gtcctgagga gcacacaagc tgggcgcacc cgactccgag acccccagcc cctgaaccct  
541 tcgtggcccc tgccctggcc ccgggactcg ctcccaaggc tcagccctcg tactccgact  
601 cgcgagcggg ctccgtaggg ggcttcttcc cgcggggcgg gcttgcggtg cccgcagctc  
661 caggcgcccc ctatgggctg ctgtcgggat accccgcgct gtaccccgcg ccacagtacc  
721 aaggccactt ccagctcttt cgcgggctcg cggcgccttc tgctggtccc acggcgcccc  
781 cttccttctt gaattgtctg ggacctggga ctgtggccac agaactcggg gccactgcga  
841 tcgccggaga cgcaggcttg tccccgggaa ctgcgccgcc caaacgcagc cggcgaactt  
901 tggcacctaa gaggcaggcg gcacatacgt gcgggcacga aggctgcggg aagagctaca  
961 ccaagagctc gcacctcaag gcgcacctgc gcacgcacac gggagagaag ccttatgcct  
1021 gtccttgga cggctgtgac tggaggttcg ctgcctcaga cgaactgacg cgccactacc  
1081 ggaagcacac tggacatcgt cccttctgct gtggcctctg cccacgtgct ttttcacgct  
1141 ctgaccactt agctctgcac atgaagcgtc acctctgagt gatcctgcac aaggactggg  
1201 gatgaaataa gagtggatcc aaggaccgta tcccaaaaga tgggccatta tatagtccca  
1261 cccagatcaa aaactgacca gaagaccata caaaggagcc ttcaggacaa acctcacatg  
1321 tcctcaggga gccccacaca tggccccaca gaccagcaa tatagaccac cagataaatc  
1381 aactcaaatg gaccctaga ccagaggagt gacctgtgt cctggacgca gatggactgg  
1441 ggtgagattt cctaagatct agaagggagc ttcacactgt gcccatctgc taggattgtt  
1501 gtcgttacta taaaaatttc ccatataaaa ccag (SEQ ID NO:2)

FIG. 3A

1 tttttttttt ttttttgctt aaaaaaaagc catgacggct ctcccacaat tcatcttccc  
61 tgcgccatct ttgtattatt tctaatttat tttggatgtc aaaaggcact gatgaagata  
121 ttttctcttg agtctccttc tttctaacco ggctctcccg atgtgaaccg agcgtcgtc  
181 cgcccgccgc cgccgcgcgc gccgcgcgcg cccgccccgc agcccaccat gtctcgccgc  
241 aagcaaggca aaccccagca cttaagcaaa cgggaattct cgcccgagcc tcttgaagcc  
301 attcttacag atgatgaacc agaccacggc ccgttgggag ctccagaagg ggatcatgac  
361 ctctcacct gtgggcagtg ccagatgaac ttccatttg gggacattct tatttttatc  
421 gagcacaac ggaacaatg caatggcagc ctctgcttag aaaaagctgt ggataagcca  
481 ccttcccctt caccaatcga gatgaaaaaa gcatccaatc ccgtggaggt tggcatccag  
541 gtcacgccag aggatgacga ttgtttatca acgtcatcta gaggaatttg ccccaaacag  
601 gaacacatag cagataaact tctgcactgg aggggcctct cctcccctcg ttctgcacat  
661 ggagctctaa tccccacgcc tgggatgagt gcagaatatg ccccgagggt tatttgtaaa  
721 gatgagccca gcagctacac atgtacaact tgcaaacagc cattcaccag tgcattggtt  
781 ctcttgcaac acgcacagaa cactcatgga ttaagaatct acttagaaag cgaacacgga  
841 agtcccctga ccccgcggtt tggtatccct tcaggactag gtgcagaatg tccttcccag  
901 ccacctctcc atgggattca tattgcagac aataaccct ttaacctgct aagaatacca  
961 ggatcagtat cgagagaggc ttccggcctg gcagaagggc gctttccacc cactcccccc  
1021 ctgttttagtc caccacogag acatcacttg gacccccacc gcatagagcg cctgggggag  
1081 gaagagatgg ccctggccac ccacacccg agtgcccttg acagggtgct gcggttgaat  
1141 ccaatggcta tggagcctcc cgccatggat ttctctagga gacttagaga gctggcaggg  
1201 aacacgtcta gccacccgct gtccccaggc cggcccagcc ctatgcaaag gttactgcaa  
1261 ccattccagc caggtagcaa gccgccttc ctggcgacgc cccccctccc tctctgcaa  
1321 tccgcccctc ctccctccca gcccccggtc aagtccaagt catgcgagtt ctgcggaag  
1381 acgttcaaatt ttcagagcaa cctggtggtg caccggcgca gccacacggg cgagaagccc  
1441 tacaagtgca acctgtgcga ccacgcgtgc acccaggcca gcaagctgaa gcgccacatg  
1501 aagacgcaca tgacaaaatc gtccccatg acggtcaagt ccgacgacg tctctccacc  
1561 gccagctccc cggaaccggg caccagcgac ttggtgggca gcgccagcag cgcgtcaag  
1621 tccgtggttg ccaagttcaa gagcgagaac gacccaacc tgatcccga gaacggggac  
1681 gaggaggaag aggaggacga cgaggaagag gaagaagagg aggaagagga ggaggaggag  
1741 ctgacggaga gcgagagggt ggactacggc ttcgggctga gcctggaggc ggcgcgccac  
1801 cacgagaaca gctcggggg cgcggtcgtg ggctggggc acgagagccg cgccctgcc  
1861 gacgtcatgc agggcatggt gtcagctcc atgcagcact tcagcgaggc cttccaccag  
1921 gtctggggc agaagcataa gcgcggccac ctggccgagg ccgagggcca cagggacact  
1981 tgcgacgaag actcgtggc cggcgagtcg gaccgcatag acgatggcac tgttaatggc  
2041 cgcggctgct ccccgggcga gtcggcctcg gggggcctgt ccaaaaagct gctgctgggc

**FIG. 3B**

2101 agccccagct cgctgagccc cttctctaag cgcatacaagc tcgagaagga gttcgacctg  
2161 cccccggccg cgatgcccaa cacggagaac gtgtactcgc agtggctcgc cggctacgcg  
2221 gcctccaggc agctcaaaga tcccttcctt agcttcggag actccagaca atcgcctttt  
2281 gcctcctcgt cggagcactc ctcggagaaac gggagtttgc gcttctccac aocgccggg  
2341 gagctggacg gagggatctc ggggcgcagc ggcacgggaa gtggagggag cacgccccat  
2401 attagtggtc cgggcccggg caggcccagc tcaaaagagg gcagacgcag cgacacttgt  
2461 gagtactgtg ggaaagtctt caagaactgt agcaatctca ctgtccacag gagaagccac  
2521 acgggcgaaa ggccttataa atgcgagctg tgcaactatg cctgtgcca gagtagcaag  
2581 ctcaccaggc acatgaaaac gcatggccag gtggggaagg acgtttacaa atgtgaaatt  
2641 tgtaagatgc ctttttagcgt gtacagtacc ctggagaaaac acatgaaaaa atggcacagt  
2701 gatcgagtgt tgaataatga tataaaaaact gaatagaggt atattaatac cctccctca  
2761 ctcccacctg acaccccctt tttcaccact ccccttcccc atcgccctcc agccccactc  
2821 cctgtaggat ttttttctag tcccatgtga tttaaacaaa caaacaaaaa aacagaagta  
2881 acgaagctaa gaatatgaga gtgcttgtca ccagcacacc tgtttttttt ctttttcttt  
2941 ttcttttttc tttttccttt tttttttttt tcctttatgt tctcaccggt tgaatgcatg  
3001 atctgtatgg ggcaatacta ttgcatttta cgcaaaacttt gagcctttct cttgtgcaat  
3061 aattttacatg ttgtgtatgt ttttttttaa acttagacag catgtatggg atgttatggc  
3121 tattttaaat tgtccctaata tcgttgcgtga gcaaacatgt tgcgtgttcc agttccgttc  
3181 tgagagaaaa agagagagag agagaaaaag accatgctgc atacattctg taatacatat  
3241 catgtacagt tttattttat aacgtgagga ggaaaaacag tctttggatt aaccctctat  
3301 agacagaata gatagcactg aaaaaaaatc tctatgagct aaatgtctgt ctctaaaggg  
3361 ttaaagtgtat caattggaaa ggaagaaaaa aggccttgaa ttgacaaatt aacagaaaaa  
3421 cagaacaagt ttattctatc atttggtttt aaaatatgag tgccttgat ctattaaaac  
3481 cacatcgatg gttctttcta cttgttataa acttgtagct taattcagca ttgggtgagg  
3541 taataaacct taggaactag catataatc tatattgtat ttctcacaac aatggctacc  
3601 taaaaagatg acccattatg tcctagttaa tcatcatttt tcctttagtt taattttata  
3661 aacaaaactg attataccag tataaaagct actttgctcc tggtgagagc ttaaaagaaa  
3721 tgggctgttt tgcccaaagt tttatttttt ttaaacaatg attaaattga atgtgtaatg  
3781 tgcaaaagcc ctggaacgca attaaatata ctagtaagga gttcatttta tgaagatatt  
3841 tgctttaata atgtcttttt aaaaatactg gcaccaaag aaatagatcc agatctactt  
3901 ggttgtcaag tggacaatca aatgataaac ttttaagacct tgtataccat attgaaagga  
3961 agaggetgac aataaggttt gacagagggg aacagaagaa aataatatga tttattagca  
4021 caacgtggta ctatttgcca tttaaaacta gaacaggtat ataagctaatt attgatacaa  
4081 tgatgattaa ctatgaattc ttaagacttg catttaaatg tgacattctt aaaaaagaa  
4141 gagaaagaat ttttaagagta gcagtatata tgtctgtgct ccctaaaagt tgtacttcat

## FIG. 3C

4201 ttctttttcca tacactgtgt gctatttgtg ttaacatgga agaggattca ttgtttttat  
4261 tttttattttt ttaattttttt ctttttttatt aagctagcat ctgccccagt tgggtgttcaa  
4321 atagcacttg actctgcctg tgatatctgt atctttttctc taatcagaga tacagagggt  
4381 gagtataaaa taaacctgct cagataggac aattaagtgc actgtacaat tttcccagtt  
4441 tacagggtcta tacttaaggg aaaagttgca agaagctga aaaaaaattg aacacaatct  
4501 cattgaggag catttttttaa aaactaaaaa aaaaaaaact ttgccagcca tttacttgac  
4561 tattgagctt acttacttgg acgcaacatt gcaagcgtg tgaatggaaa cagaatacac  
4621 ttaacataga aatgaatgat tgctttcgtc tctacagtgc aaggattttt ttgtacaaaa  
4681 ctttttttaa tataaatgtt aagaaaaatt ttttttaaaa aacacttcat tatgtttagg  
4741 ggggaactgc attttagggt tccattgtct tgggtgtgtt acaagacttg ttatccattt  
4801 aaaaatggta gtggaaattc tatgccttgg atacacaccg ctcttcaggt tgtaaaaaaa  
4861 aaaaacatac attggggaaa ggtttaagat tatatagtac ttaaatatag gaaaatgcac  
4921 actcatgttg attcctatgc taaaatacat ttatggtctt ttttctgtat ttctagaatg  
4981 gtatttgaat taaatgttca tctagtgtta ggcaactatag tattttatatt gaagcttgta  
5041 tttttaactg ttgcttgttc tcttaaaagg tatcaatgta ccttttttgg tagtggaaaa  
5101 aaaaaagaca ggctgccaca gtatatTTTT ttaatttggc aggataatat agtgcaaaatt  
5161 atttgtatgc ttcaaaaaaa aaaaaaagag agaaacaaaa aagtgtgaca ttacagatga  
5221 gaagccatat aatggcggtt tgggggagcc tgctagaatg tcacatggat ggctgtcata  
5281 ggggttgtag atatcctttt ttgttccttt ttctgtctgc catactgtat gcagtaactgc  
5341 aagctaataa cgttggtttg ttatgtagtg tgctttttgt ccctttcctt ctatcacctt  
5401 acattccagc atcttacctt catatgcagt aaaagaaaga aagaaaaaaa aaggaaaaaa  
5461 aaaaaaaaac caatgttttg cagttttttt cattgccaaa aactaaatgg tgctttatat  
5521 ttagattgga aagaatttca tatgcaaagc atattaaaga gaaagccgc tttagtcaat  
5581 acttttttgt aaatggcaat gcagaatatt ttgttattgg ccttttctat tcctgtaatg  
5641 aaagctgttt gtcgtaactt gaaattttat cttttactat gggagtcact atttattatt  
5701 gcttatgtgc cctgttcaaa acagaggcac ttaatttgat cttttatttt tctttgtttt  
5761 tatttttttt tttatttaga tgaccaaagg tcattacaac ctggcttttt attgtatttg  
5821 tttctgggtc ttgttaagtt ctattggaaa aaccactgtc tgtgtttttt tggcagttgt  
5881 ctgcattaac ctgttcatac acccattttg tccctttatt gaaaaaataa aaaaaattaa  
5941 agtaca (SEQ ID NO:3)

FIG. 4A

1 tttttttttt ttttttgctt aaaaaaaagc catgacggct ctcccacaat tcattcttccc  
61 tgcgccatct ttgtattatt tctaatttat ttgggatgtc aaaaggcact gatgaagata  
121 ttttctctgg agtctccttc tttctaaccg ggctctcccg atgtgaaccg agccgtcgtc  
181 cgcgcgcgcg cgcgcgcgcg gccgcgcgcg ccgcgcgcgc agcccaccat gtctcgccgc  
241 aagcaaggca aaccccagca cttaagcaaa cgggaattct cgcgcgagcc tcttgaagcc  
301 attcttacag atgatgaacc agaccacggc ccgttgggag ctccagaagg ggatcatgac  
361 ctctcacct gtgggcagtg ccagatgaac tcccattgg gggacattct tttttttatc  
421 gagcaciaaac ggaaacaatg caatggcagc ctctgcttag aaaaagctgt ggataagcca  
481 ccttccccctt caccaatcga gatgaaaaaa gcatccaatc ccgtggagggt tggcatccag  
541 gtcacgccag aggatgacga ttgtttatca acgtcatcta gaggaatttg ccccaaacag  
601 gaacacatag cagataaact tctgactgg aggggcctct cctcccctcg ttctgcacat  
661 ggagctctaa tccccacgcc tgggatgagt gcagaatatg cccgcagggg tatttgtaaa  
721 gatgagccca gcagctacac atgtacaact tgcaaacagc cattcaccag tgcattggtt  
781 ctcttgcaac acgcacagaa cactcatgga ttaagaatct acttagaaag cgaacacgga  
841 agtcccctga cccgcggggt tggatatcct tcaggactag gtgcagaatg tccttcccag  
901 ccacctctcc atgggattca tattgcagac aataaccctt ttaacctgct aagaatacca  
961 ggatcagtat cgagagaggc ttccggcctg gcagaagggc gctttccacc cactcccccc  
1021 ctgttttagtc caccaccgag acatcacttg gacccccacc gcatagagcg cctggggggcg  
1081 gaagagatgg ccctggccac ccatcaccgg agtgcctttg acagggtgct gcgggtgaat  
1141 ccaatggcta tggagcctcc cgccatggat ttctctagga gacttagaga gctggcaggg  
1201 aacacgtcta gccaccgct gtccccaggc cggcccagcc ctatgcaaag gttactgcaa  
1261 ccattccagc caggtagcaa gccgcccttc ctggcgacgc cccccctccc tcctctgcaa  
1321 tccgcccctc ctcccctcca gcccccggtc aagtccaagt catgcgagtt ctgcggaag  
1381 acgttcaaatt ttcagagcaa cctggtggtg caccggcgca gccacacggg cgagaagccc  
1441 tacaagtgca acctgtgcga ccacgcgtgc acccaggcca gcaagctgaa gcgccacatg  
1501 aagacgcaca tgcacaaatc gtcccccatg acgggtcaagt ccgacgacgg tctctccacc  
1561 gccagctccc cggaaccggg caccagcgac ttgggtgggca gcgccagcag cgcgctcaag  
1621 tccgtggtgg ccaagttaa gagcgagaac gacccaacc tgatcccga gaacggggac  
1681 gaggaggaag aggaggacga cgaggaagag gaagaagagg aggaagaggg ggaggaggag  
1741 ctgacggaga gcgagagggt ggactacggc ttcggtgctga gcctggaggc ggcgcgccac  
1801 cacgagaaca gctcgcgggg cgcggtcgtg ggcgtgggag acgagagccg cgccctgcc  
1861 gacgtcatgc agggcatggt gtcagctcc atgcagcact tcagcgaggc cttccaccag  
1921 gtcttgggag agaagcataa gcgcggccac ctggccgagg ccgagggcca cagggacact  
1981 tgcgacgaag actcgggtggc cggcgagtcg gaccgcatag acgatggcac tgttaatggc  
2041 cgcggctgct ccccgggcga gtcggcctcg gggggcctgt ccaaaaagct gctgctgggc

**FIG. 4B**

2101 agccccagct cgctgagccc cttctctaag cgcatacaagc tcgagaagga gttcgacctg  
2161 cccccggccg cgatgcccac caggagaaac gtgtactcgc agtggctcgc cggctacgcg  
2221 gcctccaggc agctcaaaga tcccttcctt agcttcggag actccagaca atcgcttttt  
2281 gcctcctcgt cggagcactc ctcggagaaac gggagtttgc gcttctccac accgcccggg  
2341 gagctggacg gagggatctc ggggagcagc ggcacgggaa gtggaggag cagccccat  
2401 attagtggc cggggccggg caggcccagc tcaaaagagg gcagacgcag cgacacttgt  
2461 tcttcacaca ccccattcgc gcgtagtacc cagagagctc aagatgtgtg gcagttttcg  
2521 gatggaagct cgagagccct taagtcttga gaaaatttga agccccagg ggtggggtgg  
2581 acgcgtgccg ccagtcgac gtcagcgtgg tctgtcatcc tgctagtttg tgatgttttc  
2641 tgacagtagc ctccaagaag ccgttgtgagc aagacagagt cctgcagagt cctccagcc  
2701 taggcctgca ggcctatttt atttataattt ttttaataaaa agtaaaaaca aaaaaacaga  
2761 cccacattgg aacagtgaat cagtcccata gagagggccc gtggaccatc gctgtcatga  
2821 gtgatgccct ggcccttctg aaaccagcca acctaattac ctgtattgtg gaaatgcgca  
2881 tgagtcccca accccttggt tctatacatt ctatgttgct ttttaaaaag tgtgtttaac  
2941 attgacacaa taaatgttgg agcttttagt ggtgtttgct tgttctttaa tttttaatgc  
3001 ttataagaca atgaggctgc ttatgatttt gtacttctgt acctgtttcc tacagacacc  
3061 catcgggtgg gtaggaggaa cagatttgag aaatgggcag gagatgtagg aggggaacta  
3121 ggttaccgct tatcagatgg cataaatttt caaggagaat caaaatgcaa aacttgggaa  
3181 taaatcatag caatatcata attaatgtag tagtaatatt gctgtttatt aatgctgaag  
3241 tgtgtgttttc ctaactgtct gacttataat ttgcatacca ttaaataatg cataatatgg  
3301 cagccgaat cctgtttttc aaatatatgc ttttggtggc taccatgcag gatttgaatt  
3361 tgtcttttaa tttagcttag gaaagaacat cactgggcga gcggtaaatc cttaaagaag  
3421 tgataaatgt cagtagtttc ttattaaata ttctaatttt aggttcccaa accttcagga  
3481 aatatatctt aatgcagaca aacaaacata aaacttcttt agtacttaca tcaggaaatt  
3541 tggggcagat tttagagggg ggaaattata ggaggaaaga agttcacatc agaacagaca  
3601 atcacagcaa tgctctattc cttagaaatt agtgccacaa ataagttaca tctacaaaca  
3661 ggtggtaaaa attctttctg gccaggttaa tttgcacaga acttttctca gtttggattt  
3721 ttttactgct tggagatcca gaagagaatt agaaacaaca tagcaaatta aaataggttt  
3781 gtcaataata gagctcagac acctgtgtgc tgtagattca catacaggcc gtgaacctaa  
3841 gtggggaaaa tctacctat ccaccttctg gctagattac ctagcttagt gaaaagatag  
3901 ccaataaatt ggcagtgaat ttatttctg cttattcata ataaataatg actgtcta

(SEQ ID NO:4)

FIG. 5A

1 tttttttttt ttttttgctt aaaaaaaagc catgacggct ctcccacaat tcatcttccc  
61 tgcgccatct ttgtattatt tctaatttat tttggatgtc aaaaggcact gatgaagata  
121 ttttctctgg agtctccttc tttctaaccg ggctctcccg atgtgaaccg agccgtcgtc  
181 cgcccgccgc cgccgcgcgc gccgcgcgcg cccgccccgc agcccaccat gtctcgcgc  
241 aagcaaggca aaccccagca cttaagcaaa cggaattct cgcccgagcc tcttgaagcc  
301 attcttacag atgatgaacc agaccacggc ccgttgggag ctccagaagg ggatcatgac  
361 ctctcacct gtgggcagtg ccagatgaac ttcccattgg gggacattct tttttttatc  
421 gagcaciaaac ggaaacaatg caatggcagc ctctgcttag aaaaagctgt ggataagcca  
481 ccttcccctt caccaatcga gatgaaaaaa gcatccaatc ccgtggaggt tggcatccag  
541 gtcacgccag aggatgacga ttgtttatca acgtcatcta gaggaatttg ccccaaacag  
601 gaacacatag cagataaact tctgcactgg aggggcctct cctcccctcg ttctgcacat  
661 ggagctctaa tccccacgcc tgggatgagt gcagaatatg ccccgaggg tatttgtaaa  
721 gatgagccca gcagctacac atgtacaact tgcaaacagc cattcaccag tgcattggtt  
781 ctcttgcaac acgcacagaa cactcatgga ttaagaatct acttagaaag cgaacacgga  
841 agtcccctga ccccgcggtt tcttcacaca ccccattcg gcgtagtacc cagagagctc  
901 aagatgtgtg gcagttttcg gatggaagct cgagagccct taagttctga gaaaatttga  
961 agccccagc ggtgggtgtg acgctgccc cccagtcgac gtcagcgtg tctgtcatcc  
1021 tgctagtgtt tgatgttttc tgacagtagc ctccaagaag ccgttggtgc aagacagagt  
1081 cctgcagagt ccttcacgcc taggcctgca gcgccatttt atttatattt tttaataaaa  
1141 agtaaaaaaca aaaaaacaga cccacattgg aacagtgaat cagtcccata gagagggccc  
1201 gtggaccatc gctgtcatga gtgatgcctt ggcccttctg aaaccagcca acctaatatc  
1261 ctgtattgtg gaaatgcgca tgagtcccca accccttggt tctatacatt ctatgttgct  
1321 ttttaaaaag tgtgcttaac attgacacaa taaatggttg agcttttagt ggtgtttgct  
1381 tgttctttta tttttaatgc ttataagaca atgaggtgc ttatgatttt gtacttctgt  
1441 acctgtttcc tacagacacc catcgggttg gtaggaggaa cagatttgag aaatgggcag  
1501 gagatgtagg aggggaacta ggttaccgct tatcagatgg cataaatttt caaggagaat  
1561 caaatgcaa aacttgggaa taaatcatag caatatcata attaatgtag tagtaatatt  
1621 gctgtttatt aatgctgaag tgtggttttc ctaactgtct gacttataat ttgcatacca  
1681 ttaaataatg cataatatgg cacgccgaat cctgtttttc aaatatatgc ttttggtggc  
1741 taccatgcag gatttgaatt tgtcttttaa tttagcttag gaaagaacat cactgggcga  
1801 gcggtaaatc ctaaagaagg tgataaatgt cagtagtttc ttattaaata ttctaatttt  
1861 aggttcccaa accttcagga aatatatctt aatgcagaca acaaacata aaacttcttt  
1921 agtacttaca tcaggaaatt tggggcagat tttagagggg ggaaattata ggaggaaaga  
1981 agttcacatc agaacagaca atcacagcaa tgctctattc cttagaaatt agtgccacaa  
2041 ataagttaca tctacaaaca ggtggtaaaa attctttctg gccagttaa tttgcacaga

**FIG. 5B**

2101 acttttctca gtttggtatt ttttactgct tggagatcca gaagagaatt agaaacaaca  
2161 tagcaaatta aaatagggtt gtcaataata gagctcagac acctgtgtgc tgtagattca  
2221 catacaggcc gtgaacctaa gtgggggaaaa tcctacctat ccaccttctg gctagattac  
2281 ctagcttagt gaaaagatag ccaaataatt ggcatgtgaa ttatttcctg cttattcata  
2341 ataaataatg actgtcta (SEQ ID NO:5)

FIG. 6A

1 gacgttcaag ttcgcagggga cgtcacgtcc gcacttgaac ttgcagctca ggggggcttt  
61 tgccatTTTT ttcattctctc tctctccctc tateccctctt ctctcttccct ctctctcttt  
121 ttttttctta aaaaaaaaaa agccatgacg gctctcccac aattcatctt ccctgcgccca  
181 tcttttgtatt atttctaatt tattttggat gtcaaaaggc actgatgaag atattttctc  
241 tggagtctcc ttctttctaa ccggtctctc ccgatgtgaa ccgagccgtc gtccgcacgc  
301 cgccgcgcgc gccgcgcgcc gccccgcagc ccaccatgtc tcgccgcaag caaggcaaac  
361 cccagcactt aagcaaacgg gaattctcgc ccgaacctct tgaagccatt cttacagatg  
421 atgaaccaga ccatggcccg ttgggagctc cagaagggga ccacgacctt ctcaacctgtg  
481 ggcagtgccg gatgaatttc ccactggggg acattcttat ttttatcgag cacaaacgga  
541 aacaatgcaa tggcagcctc tgcttagaaa aagggtgtgga taagccgcct tccccctctc  
601 ccategagat gaaaaaggca tccaatcctg tggagggttg catccaggtc acgccagagg  
661 atgacgattg tttatcaacg tcatctagag gaatttgccc caaacaggaa cacatagcag  
721 ataaacttct gcactggagg ggctgtctc ctctcggtc tgcacacgga gctctaattc  
781 ccacgcccgg gatgagtgcg gaatatgcc cgcagggtat ttgtaaagat gagcccagca  
841 gctacacatg tacaacttgc aaacagccat tcaccagtgc atggtttctc ttgcaacacg  
901 cacagaacac tcatggatta agaatctact tagaaagtga acacggaagt cccctgacct  
961 cgcggggttg tatcccttca ggactagggtg cagaatgtcc ttcccagcca cctctccatg  
1021 ggattcatat tgcaacaat aaccccttta acctgctaag aataccagga tcagtatcga  
1081 gagaggcttc cggcctggca gaaggcgct ttcacccac tccccccctg tttagtccac  
1141 caccgagaca tcaattggac ccccaccgca tagagcgctt gggggcgga gagatggccc  
1201 tggccacca tcacccgagt gcctttgaca ggggtgctgcg gttgaatcca atggtatgg  
1261 agcctcccgc catggatttc tctaggagac ttagagagct ggcagggaac acgtctagtc  
1321 caccgctgtc cccaggccgg cccagtccta tgcaaagggt actgcaacca ttccagccag  
1381 gtagcaagcc acccttccctg gcgacgcccc cctccctcc ctctgcaatcc gcccctctc  
1441 cctcccaacc cccggtcaag tccaagtcat gcgagttctg cggcaagacg ttcaaatttc  
1501 agagcaactt ggtggttcac cgacgcagcc atactggtga gaagccctat aagtgaacc  
1561 tgtgcgacca cgcgtgcaca caggccagca agctgaagcg tcacatgaag acacacatgc  
1621 acaaatcgtc ccccatgaca gtcaagtccg acgatggcct ctccacagcc agctccccgg  
1681 aacctggtac cagcgacctg gtgggcagcg ccagcagtgc gctcaagtca gtggtggcca  
1741 agttcaagag tgagaacgac cccaacttga tcccagagaa cggggatgag gaggaagagg  
1801 aggacgacga ggaagaagaa gaagaggagg aagaggagga ggaggagctg acggagagcg  
1861 agaggggtgga ctacggcttc gggctgagcc tggaggctgc acgccacctt gagaacagct  
1921 ctcggggcgc agtgggtggc gtgggcgacg agggccgcgc cctgcccgat gtcattgcagg  
1981 gcatgggtgt cagctccatg cagcacttca gcgaggcctt ccaccaggtc ctgggcgaaa  
2041 agcataagcg tagccacctg gccgaggccg agggccatag ggacacttgt gatgaagact

**FIG. 6B**

2101 cgggtggccgg tgagtcagac cgcataagac atggcactgt taatgggtcgt ggctgctccc  
2161 ccggcgaatc ggcttcgggg ggtctgtcca aaaagctgct gctgggtagc ccagctcgc  
2221 tgagcccctt ctccaagcgc atcaagctgg agaaggagtt tgacctgccc ccggccgcga  
2281 tgcctaacac ggagaacgtg tattcgcagt ggctcgctgg ctatgcggcc tccaggcagc  
2341 tcaaagatcc cttccttact ttccgagact ccagacaatc gccttttgcc tctcatcag  
2401 agcactcctc ggagaacggg agcttgctgt tctccacacc gcccggggag ctggacggag  
2461 ggatctcagg gcgcagcggc acaggaagtg gagggagcac gcccattatt agtgggtccg  
2521 gcccgggcag gccagctca aaagagggca gacgcagcga cacttgtcct tcacacaccc  
2581 ccgttcggcg tagtaccocg cgagctcaag atgtgtggca gttttcggat ggaagctcaa  
2641 gaacccttaa gttctgagaa actttgaagc cccaagggc gggcgggaca tgcgcgccc  
2701 agccgacgtc aacgtgctcc gttatcctgc tagattgtga tgttttctga cagtagcctc  
2761 caagaagaca agagtccctc cgagtcctcc cagcctgggc ctgcagtgcc attttattta  
2821 ttttttttaa taaaacgtaa aaacaaaaaa aaccagaccc acattggaac agtgaaccg  
2881 tcccatccag agggccctag gactgccgca gttggagcga cgtccaaccc ttttgaaacc  
2941 agccaacctt attaccgta ctgtggaaat gagcatgacc cctgaccctt tgtttctata  
3001 cattctatgt tgtcttttaa aaagtgtgct taacattgac ataataaatg ttggagcttt  
3061 aggcgggtgtg tgcttgtttt ttaattttta atgctcgtaa gacaatgtgg ctgcttcagg  
3121 ctttatgtct gtgtactttt ttctcttcag aagctcatag ggtgagcaga aggaccagac  
3181 tcaagtcca ggcaggagac ctagaaaagg aagtaggctt ttcagatggc atacattttc  
3241 aaagaaaatc aaaatgcaaa gctaggggat aatcatagt aatatcataa ttaatgtagt  
3301 agtattgctg tttattaatg ctgacgtgtg tttttcctct ctgacttata atttgcatac  
3361 cattaaataa tgcataaata tggcacactg aatccttttt caaatacacg cttttggtga  
3421 ctacc (SEQ ID NO: 6)

FIG. 7

1 gacgttcaag ttgcgaggga cgtcacgtcc gcacttgaac ttgcagctca ggggggcttt  
61 tgccattttt ttcatctctc tctctccctc tatccctctt ctctcttctt ctctctcttt  
121 tttttcctta aaaaaaaaaa agccatgacg gctctccac aattcatctt cctgcgcca  
181 tctttgtatt atttctaatt tattttggat gtcaaaaggc actgatgaag atattttctc  
241 tggagtctcc ttctttctaa cccggctctc ccgatgtgaa ccgagccgtc gtccgcacgc  
301 cgccgcgcgc gccgcgcgcc gccccgcgc ccaccatgtc tcgcccgaag caaggcaaac  
361 cccagcactt aagcaaacgg gaattctcgc ccgaacctct tgaagccatt cttacagatg  
421 atgaaccaga ccatggcccg ttgggagctc cagaagggga ccacgacctt ctcacctgtg  
481 ggcagtgcc aatgaatttc ccactggggg acattcttat ttttatcgag caciaaacgga  
541 aacaatgcaa tggcagcctc tgcttagaaa aaggtgtgga taagccgcct tccccctctc  
601 ccacgcagat gaaaaaggca tccaatcctg tggagggttg catccaggtc acgccagagg  
661 atgacgattg tttatcaacg tcatctagag gaatttgccc caaacaggaa cacatagcag  
721 ataaaacttct gactggagg ggctgtcct ctctcggtc tgcacacgga gctctaattc  
781 ccacgcccgg gatgagtgc gaatatgcc cgcagggtat ttgtaaagat gagcccagca  
841 gctacacatg tacaacttgc aaacagccat tcaccagtgc atggtttctc ttgcaacacg  
901 cacagaacac tcatggatta agaattctact tagaaagtga acacggaagt cccctgacct  
961 cgcgggtcct tcacacaccc ccgttcggcg tagtacctcg cgagctcaag atgtgtggca  
1021 gttttcggat ggaagctcaa gaaccttaa gttctgagaa actttgaagc ccccaagggc  
1081 ggggcggaca tgcgcgcgcc agccgacgtc aacgtgctcc gttatcctgc tagattgtga  
1141 tgttttctga cagtagcctc caagaagaca agagtcctgc cgagtcctcc cagcctgggc  
1201 ctgcagtgcc attttattta ttttttttaa taaaacgtaa aaacaaaaaa aaccagacct  
1261 acattggaac agtgaaccgg tcccatccag agggccctag gactgcgcga gttggagcga  
1321 cgtccaacct ttttgaaacc agccaacctt attacctgta ctgtggaaat gagcatgacc  
1381 cctgacctct tgtttctata cattctatgt tgtcttttaa aaagtgtgct taacattgac  
1441 ataataaatg ttggagcttt aggcgggtgtg tgcttgtttt ttaattttta atgctcgtaa  
1501 gacaatgtgg ctgcttcagg ctttatgtct gtgtactttt tttccttcag aagctcatag  
1561 ggtgagcaga aggaccagac tcaagtgcc ggcaggagac ctagaaaagg aagtaggctt  
1621 ttcagatggc atacattttc aaagaaaatc aaaatgcaa gctaggggat aatcatagt  
1681 aatatcataa ttaatgtagt agtattgctg tttattaatg ctgacgtgtg tttttcctct  
1741 ctgacttata atttgcatac cattaataaa tgcataaata tggcacactg aatccttttt  
1801 caaatacacg ctttttgtga ctacc (SEQ ID NO: 7)

**FIG. 8**

1 agagcagacg cggcgcgcgga cgggtgtgaag ttacagcccc gccagccgaa cctcttgaag  
61 ccatttcttac agatgatgaa ccagaccatg gcccgttggg agctccagaa ggggaccacg  
121 accttctcac ctgtgggcag tgccagatga atttccact gggggacatt cttattttta  
181 tcgagcacia acggaaacia tgcaatggca gcctctgctt agaaaaaggt gtggataagc  
241 cgccttcccc ttctcccatc gagatgaaaa aggcattcaa tcctgtggag gttggcatcc  
301 aggtcacgcc agaggatgac gattgtttat caacgtcatc tagaggaatt tgcccaaac  
361 aggaacacat agcagataaa cttctgcact ggaggggcct gtcctctcct cggctctgcac  
421 acggagctct aatccccacg cccgggatga gtgcagaata tgccccgag ggtatttcta  
481 aagatgagcc cagcagctac acatgtacaa cttgcaaca gccattcacc agtgcattgt  
541 ttctcttgca acacgcacag aacactcatg gattaagaat ctacttagaa agtgaacacg  
601 gaagtccctt gaccccgcg gtccttcaca ccccccggt cggcgtagta ccccgcgagc  
661 tcaagatgtg tggcagtttt cggatggaag ctcaagaacc cttaagttct gagaaacttt  
721 gaagccccca agggcggggc ggacatgcgc cgcccagccg acgtcaacgt gctccgttat  
781 cctgctagat tgtgatgttt tctgacagta gcctccaaga agacaagagt cctgccagat  
841 cctcccagcc tgggcctgca gtgccatttt atttatattt tttaataaaa cgtaaaaaaca  
901 aaaaaaacca gaccacattt ggaacagtga acccgccca tccagagggc cctaggactg  
961 cgcagtttgg agcgacgtcc aacccttttg aaaccagcca acctaattac cgtactgtg  
1021 gaaatgagca tgacccctga ccccttgttt ctatacatte tatgttgtct tttaaaaagt  
1081 gtgcttaaca ttgacataat aaatgttga gctttaggcg gtgtgtgctt gttttttaat  
1141 ttttaatgct cgtaagacia tgtggctgct tcaggcttta tgtctgtgta ctttttttcc  
1201 ttcagaagct catagggtga gcagaaggac cagactcaag tgccaggcag gagacctaga  
1261 aaaggaagta ggcttttcag atggcataca ttttcaaaga aaatcaaat gcaaagctag  
1321 gggataaatc atagtaatat cataattaat gtagtagtat tgctgtttat taatgctgac  
1381 gtgtgttttt cctctctgac ttataatttg cataccatta aataatgcat aaatatggca  
1441 cactgaatcc tttttcaaat acacgttttt ggtgactacc (SEQ ID NO:8)

FIG. 9A

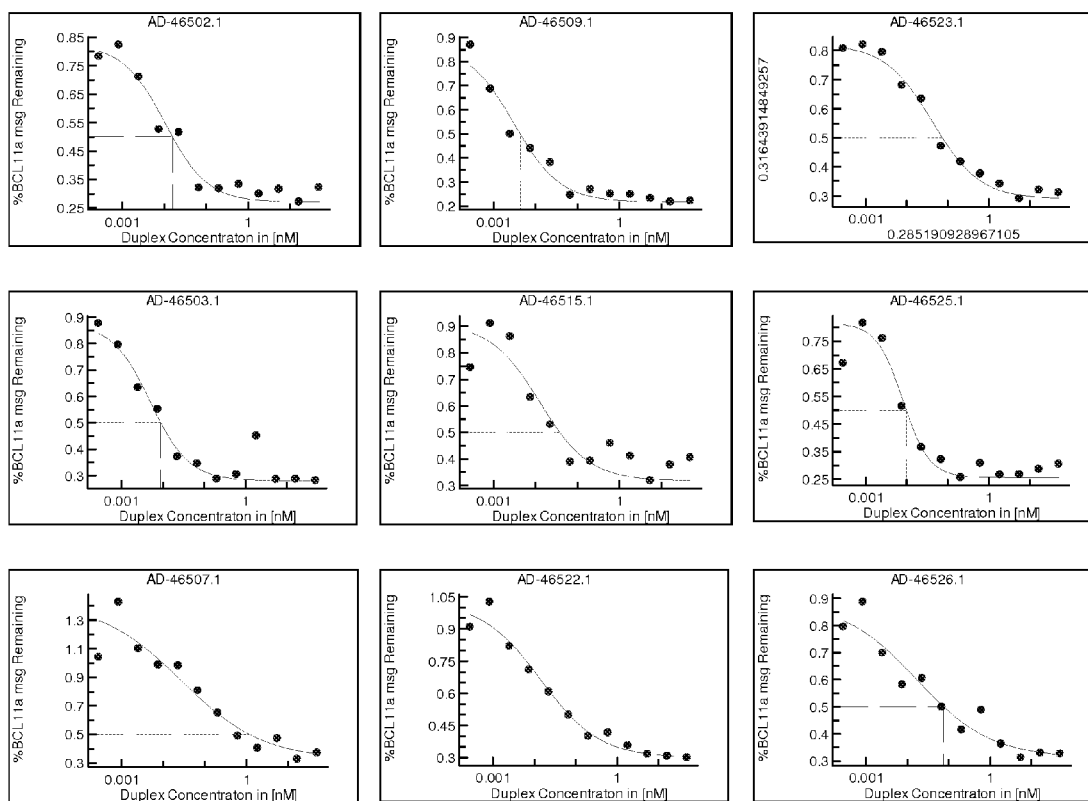


FIG. 9B

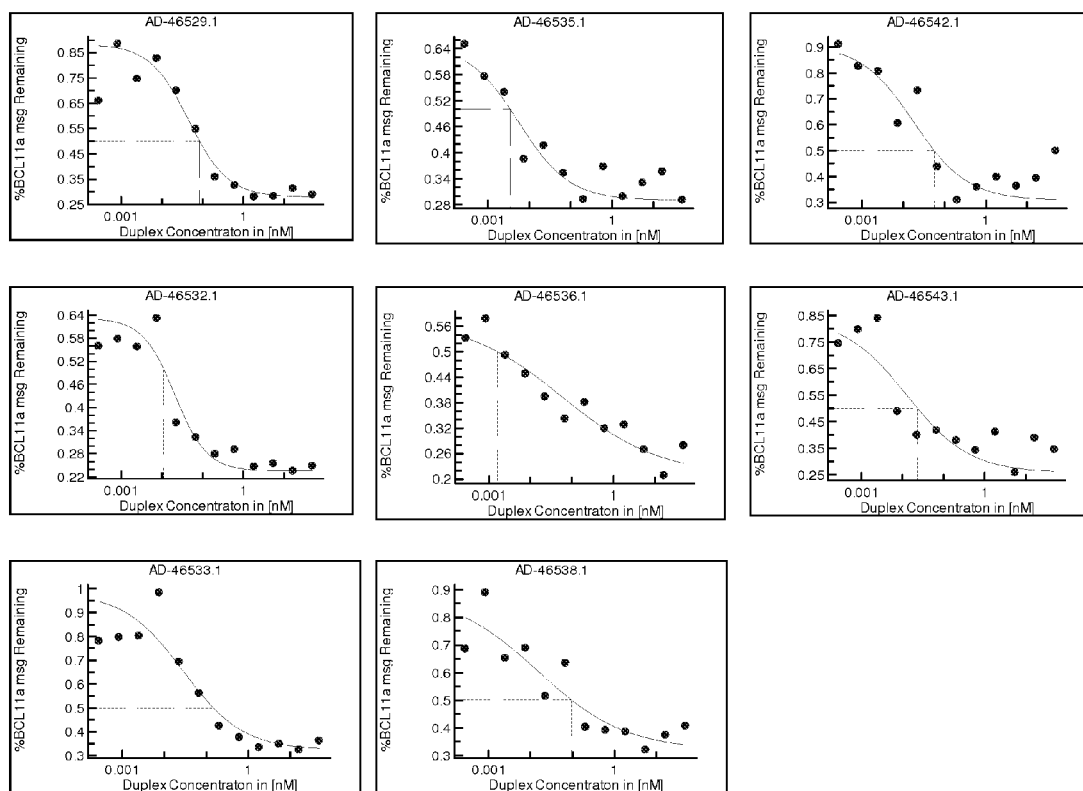


FIG. 9C

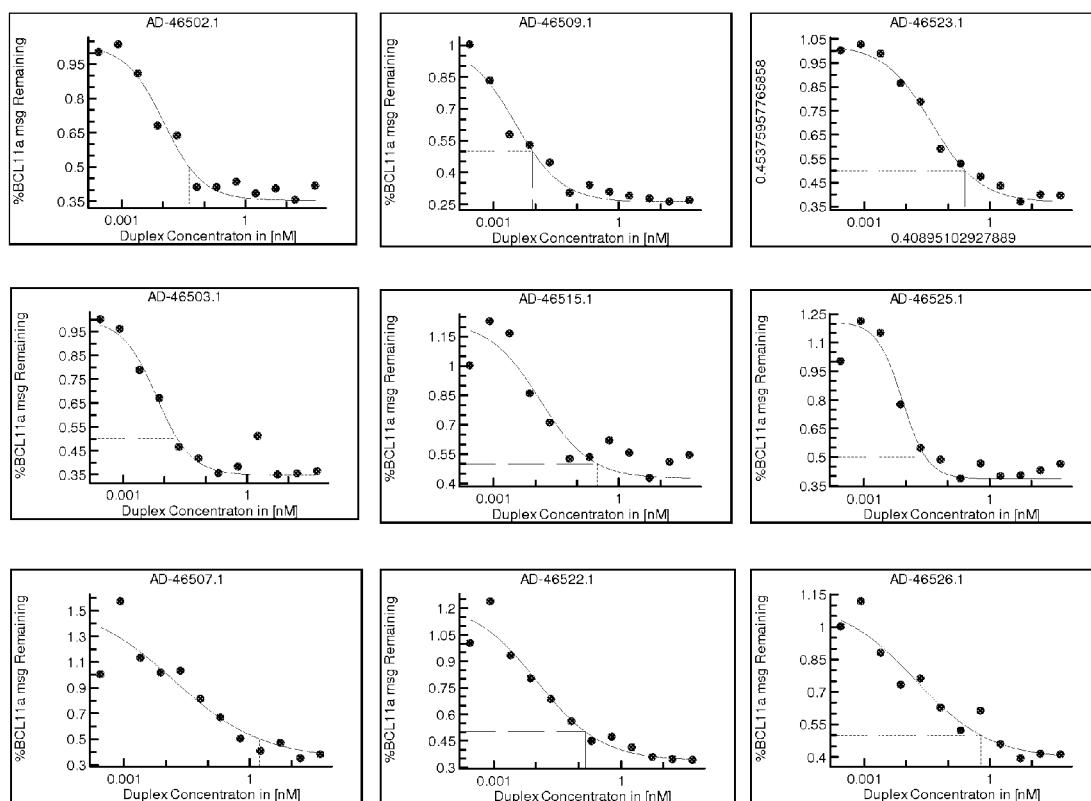
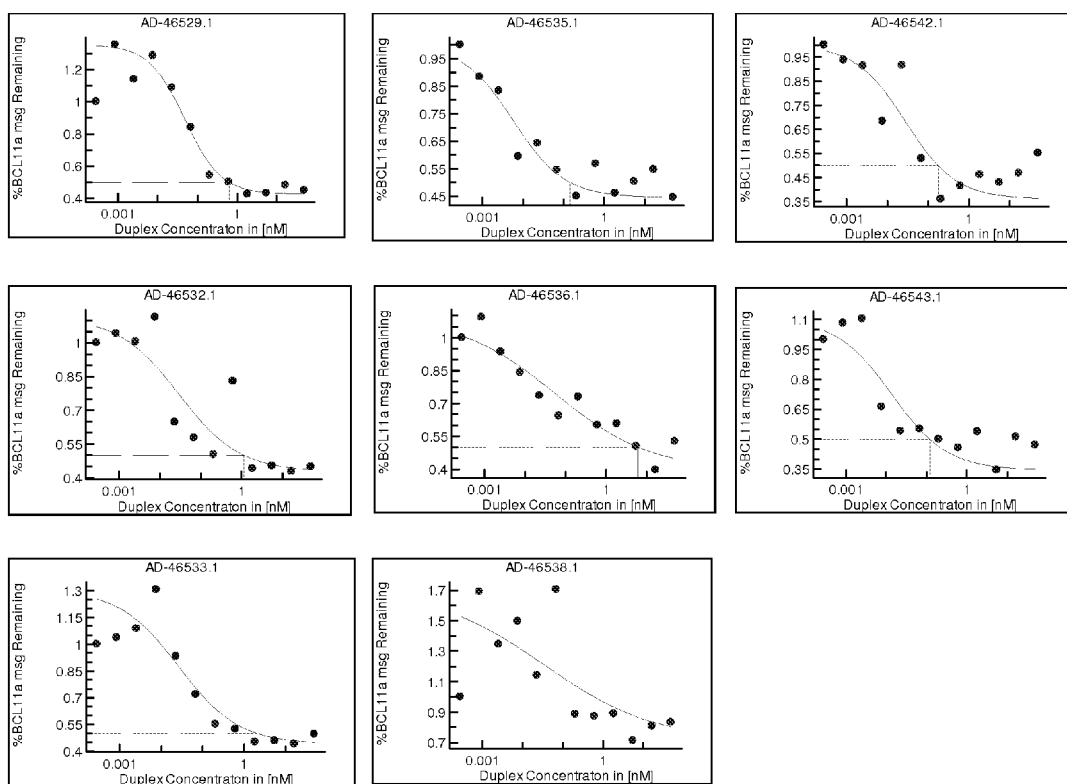


FIG. 9D



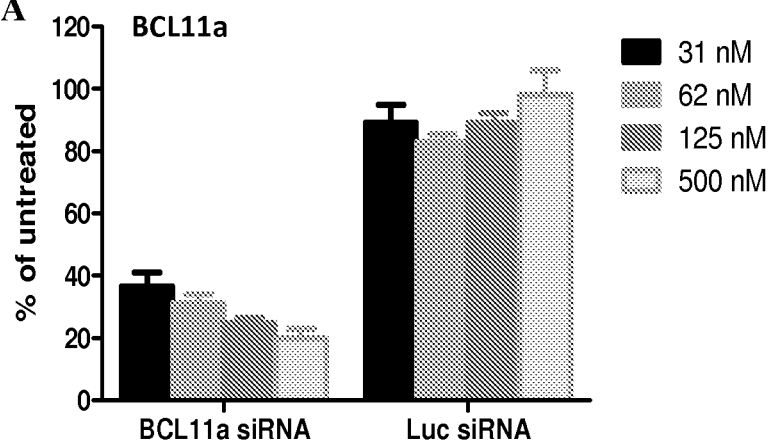
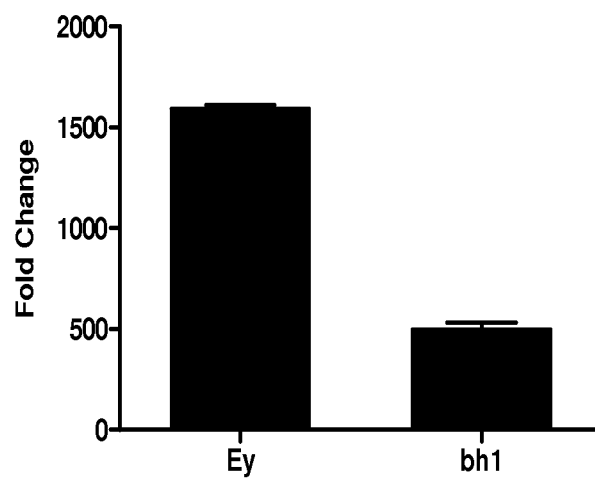
**FIG. 10A****FIG. 10B**

FIG. 11A

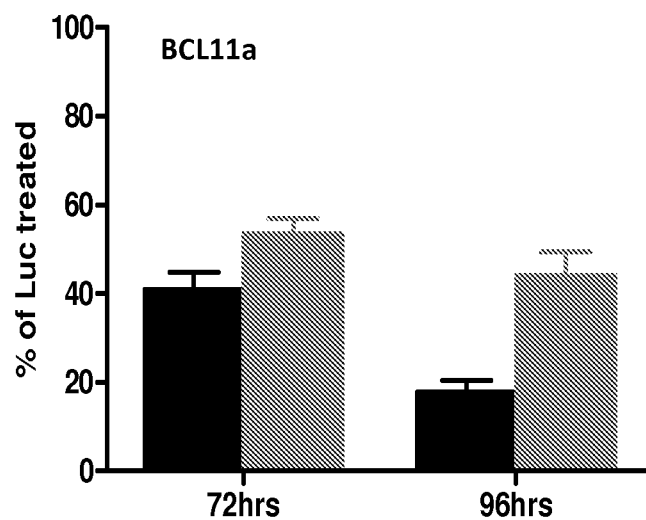


FIG. 11B

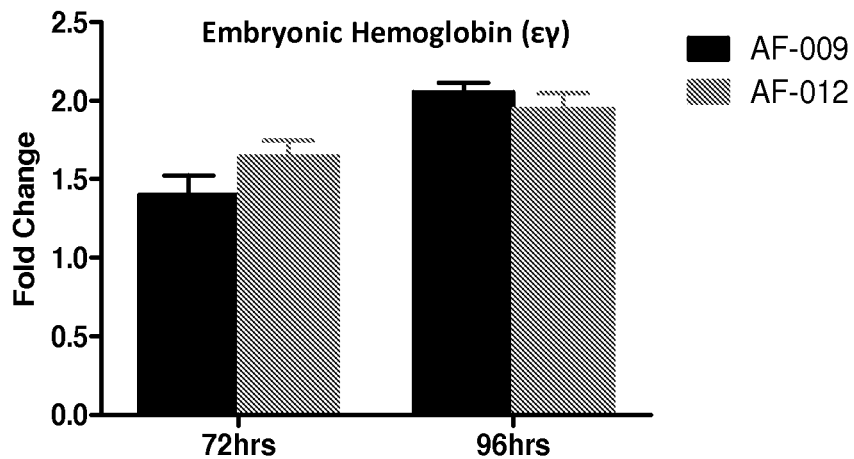


FIG. 12A

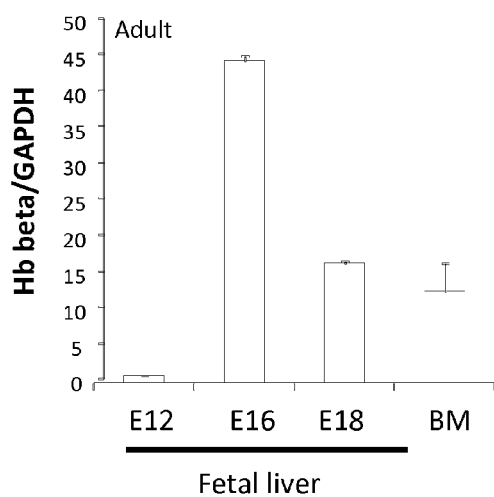


FIG. 12B

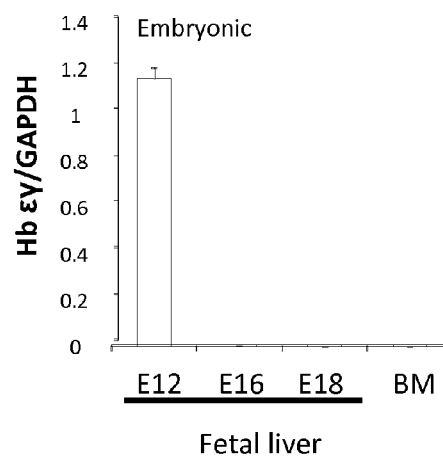


FIG. 12C

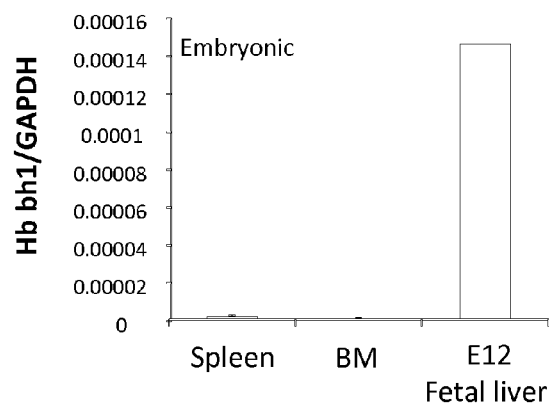


FIG. 13A

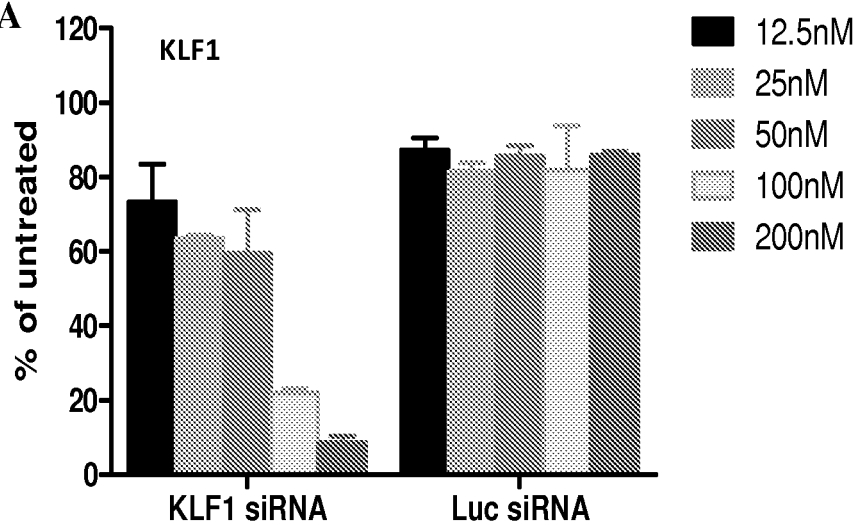


FIG. 13B

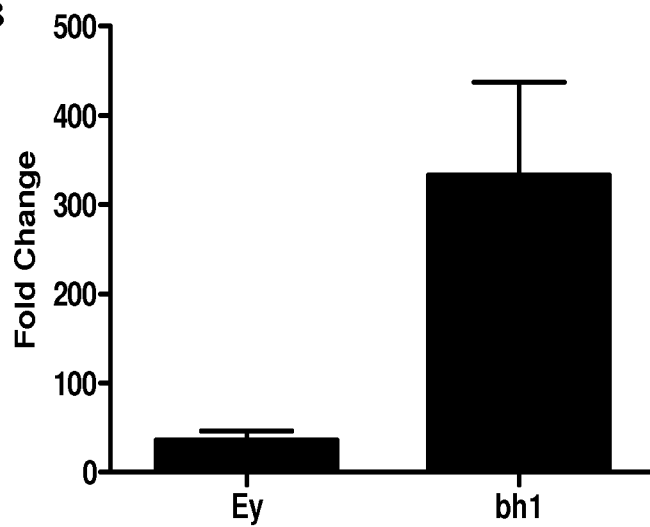


FIG. 14A

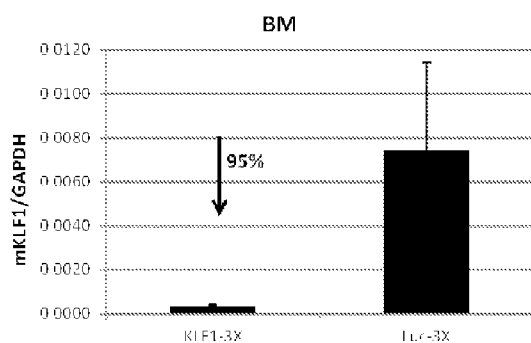


FIG. 14C

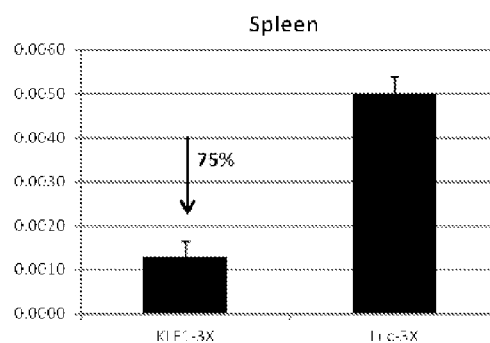


FIG. 14B

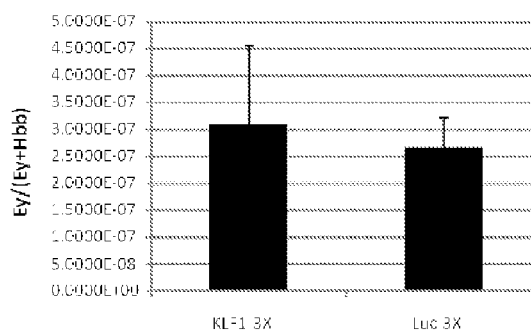


FIG. 14D

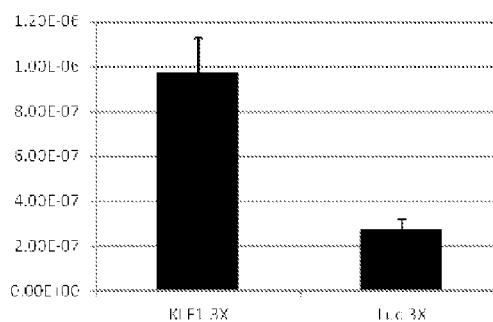


FIG. 14E



1

# COMPOSITIONS AND METHODS FOR INHIBITING EXPRESSION OF KLF-1 AND BCL11A GENES

## CROSS REFERENCE TO RELATED APPLICATIONS

This application is the U.S. National Phase Application under 35 U.S.C. §371 of International Application No. PCT/US 2011/064275, filed Dec. 9, 2011, which claims the benefit of priority to U.S. Provisional Application Ser. No. 61/422,049, filed on Dec. 10, 2010, the contents of which are hereby incorporated by reference in their entirety.

## FIELD OF THE INVENTION

The invention relates to the specific inhibition of the expression of the KLF1 and BCL11A genes.

## BACKGROUND OF THE INVENTION

Normal adult hemoglobin comprises four globin proteins, two of which are alpha ( $\alpha$ ) proteins and two of which are beta ( $\beta$ ) proteins. During mammalian fetal development, particularly in humans, the fetus produces fetal hemoglobin, which comprises two  $\gamma$ -globin proteins, instead of the two  $\beta$ -globin proteins. During fetal development or infancy, depending on the particular species and individual, a globin switch occurs, referred to as the “fetal switch”, at which point, erythrocytes in the fetus switch from making predominantly  $\gamma$ -globin to making predominantly  $\beta$ -globin. The developmental switch from production of predominantly fetal hemoglobin or HbF ( $\alpha_2\gamma_2$ ) to production of adult hemoglobin or HbA ( $\alpha_2\beta_2$ ) begins at about 28 to 34 weeks of gestation and continues shortly after birth until HbA becomes predominant. This switch results primarily from decreased transcription of the  $\gamma$ -globin genes and increased transcription of  $\beta$ -globin genes.

Abnormalities in hemoglobin protein and function are associated with hemoglobinopathies. Hemoglobinopathies encompass a number of anemias of genetic origin in which there is a decreased production and/or increased destruction (hemolysis) of red blood cells (RBCs). These also include genetic defects that result in the production of abnormal hemoglobins with a concomitant impaired ability to maintain oxygen concentration. Some such disorders involve the failure to produce normal  $\beta$ -globin in sufficient amounts, while others involve the failure to produce normal  $\beta$ -globin entirely. The disorders associated with abnormalities in the  $\beta$ -globin protein are referred to generally as  $\beta$ -hemoglobinopathies. For example,  $\beta$ -thalassemias result from a partial or complete defect in the expression of the  $\beta$ -globin gene, leading to deficient or absent HbA. Sickle cell anemia results from a point mutation in the  $\beta$ -globin structural gene, leading to the production of an abnormal (sickled) hemoglobin (HbS). HbS RBCs are more fragile than normal RBCs and undergo hemolysis more readily, leading eventually to anemia (Atweh, (2001) *Semin. Hematol.* 38(4):367-73).

Kruppel-like factor 1 (erythroid) (KLF1) is a transcription factor involved in regulating adult globin expression. KLF1 is expressed in erythroid cells and positively regulates the adult  $\beta$ -globin gene. KLF1 is also an important activator of BCL11A, which encodes a suppressor of fetal hemoglobin. Loss-of-function mutations in the KLF1 gene have been associated with hereditary persistence of fetal hemoglobin (HPFH), which is characterized by persistent high levels of HbF in adults. The developmental switch from human fetal ( $\gamma$ ) to adult ( $\beta$ ) hemoglobin represents a clinically important

2

example of developmental gene regulation. The transcription factor BCL11A is a central mediator of the  $\gamma$ -globin silencing and hemoglobin switching that occurs in erythroid progenitor cells. KLF1 has been suggested to control globin gene switching by directly activating  $\beta$ -globin and indirectly repressing  $\gamma$ -globin gene expression. Knockdown of KLF1 in human and mouse adult erythroid progenitors markedly reduced BCL11A levels and increased human  $\gamma$ -globin/ $\beta$ -globin expression ratios (Zhou et al. (2010) *Nat. Genet.* 42:742-744).

The need exists for identifying novel therapeutics that modulate one or more of: fetal switch, activation of fetal hemoglobin (HbF), thus altering globin chain levels, e.g., the ratio of  $\gamma$ -globin to  $\beta$ -globin. Such therapeutics can be used to treat subjects with a variety of abnormalities in hemoglobin protein and function, such as hemoglobinopathies.

## SUMMARY OF THE INVENTION

The present invention describes methods and iRNA compositions for modulating the expression of a KLF1 gene and/or a BCL11A gene. In certain embodiments, expression of KLF1 is reduced or inhibited using a KLF-specific iRNA, thereby leading to a decreased expression of adult  $\beta$ -globin genes. Reduced expression of KLF1 gene can also negatively regulate expression of BCL11A, thus leading to higher levels of  $\gamma$  (fetal) globin relative to  $\beta$ -globin levels. Alternatively, or in combination with inhibition of KLF1 gene expression, expression of BCL11A can be reduced or inhibited using a BCL11A-specific iRNA, thereby causing higher levels of  $\gamma$  (fetal) globin relative to  $\beta$ -globin levels. Thus, inhibition of KLF1 and/or a BCL11A gene expression using an iRNA composition featured in the invention can be a useful approach to therapies aimed at reducing the expression of adult  $\beta$ -globin genes, and/or increasing fetal hemoglobin (HbF) production. Such inhibition can be useful in treating hemoglobinopathies, such as  $\beta$ -hemoglobinopathies, sickle cell disease and the  $\beta$ -thalassemias.

Accordingly, described herein are compositions and methods that effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of the KLF1 and BCL11A genes, such as in a cell or mammal. Also described are compositions and methods for treating pathological conditions and diseases caused by the expression of KLF1 and BCL11A genes, such as hemoglobinopathies, e.g.,  $\beta$ -hemoglobinopathies, sickle cell anemia and the  $\beta$ -thalassemias.

As used herein, the term “iRNA” refers to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. In one embodiment, an iRNA as described herein effects inhibition of KLF1 expression in a cell or mammal. In another embodiment, an iRNA as described herein effects inhibition of one or more transcript variants of BCL11A expression in a cell or mammal (e.g., transcript variant 1, 2, and/or 3).

The iRNAs included in the compositions featured herein encompass a dsRNA having an RNA strand (the antisense strand) having a region that is 30 nucleotides or less, generally 19-24 nucleotides in length, that is substantially complementary to at least part of an mRNA transcript of a KLF1 gene (e.g., a mouse or human KLF1 gene) (also referred to herein as a “KLF1-specific iRNA”). Alternatively, or in combination, iRNAs encompass a dsRNA having an RNA strand (the antisense strand) having a region that is 30 nucleotides or less, generally 19-24 nucleotides in length, that is substantially complementary to at least part of an mRNA transcript of a BCL11A gene (e.g., a mouse or human variant 1, 2 or 3 of a

BCL11A gene) (also referred to herein as a “BCL11A-specific iRNA”). In certain embodiments, an iRNA encompasses a dsRNA having an RNA strand (the antisense strand) having a region that is substantially complementary to exon 4 of BCL11A, e.g., exon 4 of human BCL11A variants 1-3. In one embodiment, the iRNA encompasses a dsRNA having an antisense strand comprising a region substantially complementary to at least a region of exon 4 of BCL11A variant 2, e.g., a region of exon 4 that includes nucleotides 716-2458, or a fragment thereof, of SEQ ID NO: 4 depicted in FIG. 4A-4B (e.g., a region that includes nucleotides 860-2410, or a fragment thereof, of SEQ ID NO: 4, e.g., a region of SEQ ID NO: 4 as shown in Table 4). In another embodiment, the iRNA encompasses a dsRNA having an antisense strand comprising a region substantially complementary to at least a region of exon 4 of BCL11A variant 1 (e.g., a region of exon 4 that includes nucleotides 716-5946, or a fragment thereof, of SEQ ID NO: 3 depicted in FIG. 3A-3C). In yet another embodiment, the iRNA encompasses a dsRNA having an antisense strand comprising a region substantially complementary to at least a region of exon 4 of BCL11A variant 3 (e.g., a region of exon 4 that includes nucleotides 716-858, or a fragment thereof, of SEQ ID NO: 5; depicted in FIG. 5A-5C).

In other embodiments, an iRNA encompasses a dsRNA having an RNA strand (the antisense strand) having a region that is substantially complementary to a portion of a BCL11A or KLF1 mRNA according to Tables 2A-1, 2A-2, 2A-3, 2B and 2C, and Tables 3, 4, 5, 6 and 7. In one embodiment, the iRNA encompasses a dsRNA having an RNA strand (the antisense strand) having a region that is substantially complementary to a portion of a KLF1 mRNA, e.g., a human KLF1 mRNA (e.g., a human KLF1 mRNA from nucleotides 1251-1568 of SEQ ID NO:1, or a portion thereof). In another embodiment, the iRNA encompasses a dsRNA having an RNA strand (the antisense strand) having a region that is substantially complementary to a portion of a BCL11A mRNA, e.g., a human BCL11 mRNA (e.g., a human BCL11 mRNA from nucleotides 415-720 of SEQ ID NO:1, or a portion thereof).

Thus, depending on the context, the term iRNA may refer to KLF1-specific iRNA, BCL11A-specific iRNA, or collectively to both).

In one embodiment, an iRNA for inhibiting expression of a KLF1 or BCL11A gene includes at least two sequences that are complementary to each other. The iRNA includes a sense strand having a first sequence and an antisense strand having a second sequence. The antisense strand includes a nucleotide sequence that is substantially complementary to at least part of an mRNA encoding KLF1 or a BCL11A transcript, and the region of complementarity is 30 nucleotides or less, and at least 15 nucleotides in length. Generally, the iRNA is 19 to 24, e.g., 19 to 21 nucleotides in length. In some embodiments the iRNA is from about 15 to about 25 nucleotides in length, and in other embodiments the iRNA is from about 25 to about 30 nucleotides in length. An iRNA targeting KLF1, upon contacting with a cell expressing KLF1, inhibits the expression of a KLF1 gene by at least 10%, at least 20%, at least 25%, at least 30%, at least 35% or at least 40% or more, such as when assayed by a method as described herein. In one embodiment, the iRNA targeting KLF1 is formulated in a stable nucleic acid lipid particle (SNALP). An iRNA targeting one or more transcript variants of BCL11A, upon contacting with a cell expressing the one or more transcript variants of BCL11A, inhibits the expression of a BCL11A transcript variant by at least 10%, at least 20%, at least 25%, at least 30%, at least 35% or at least 40% or more, such as when assayed by a method as described herein. In one embodiment, the iRNA

targeting a BCL11A transcript variant is formulated in a stable nucleic acid lipid particle (SNALP).

In one embodiment, an iRNA featured herein includes a first sequence of a dsRNA that is selected from the group consisting of the sense sequences of Tables 2A-1, 2A-2, 2A-3, 2B and 2C, and Tables 3, 4, 5, 6 and 7, and a second sequence that is selected from the group consisting of the corresponding antisense sequences of Tables 2A-1, 2A-2, 2A-3, 2B and 2C, and Tables 3, 4, 5, 6 and 7. The iRNA molecules featured herein can include naturally occurring nucleotides or can include at least one modified nucleotide, including, but not limited to a 2'-O-methyl modified nucleotide, a nucleotide having a 5'-phosphorothioate group, and a terminal nucleotide linked to a cholesteryl derivative. Alternatively, the modified nucleotide may be chosen from the group of: a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide. Generally, such a modified sequence will be based on a first sequence of said iRNA selected from the group consisting of the sense sequences of Tables 2A-1, 2A-2, 2A-3, 2B and 2C, and Tables 3, 4, 5, 6 and 7, and a second sequence selected from the group consisting of the corresponding antisense sequences of Tables 2A-1, 2A-2, 2A-3, 2B and 2C, and Tables 3, 4, 5, 6 and 7.

In one embodiment, an iRNA featured herein includes a sense sequence of a KLF1 dsRNA selected from the group consisting of SEQ ID NO:89, SEQ ID NO:55, SEQ ID NO:33, SEQ ID NO:79 and of SEQ ID NO:63; and an antisense sequence of a KLF1 dsRNA selected from the group consisting of SEQ ID NO:90, SEQ ID NO:56, SEQ ID NO:34, SEQ ID NO:80 and SEQ ID NO:64. In another embodiment, an iRNA featured herein includes a sense sequence of a KLF1 dsRNA selected from the group consisting of SEQ ID NO:558, SEQ ID NO:614, SEQ ID NO:612, SEQ ID NO:586 and of SEQ ID NO:604; and an antisense sequence of a KLF1 dsRNA selected from the group consisting of SEQ ID NO:559, SEQ ID NO:615, SEQ ID NO:613, SEQ ID NO:587 and of SEQ ID NO:605.

In one embodiment, an iRNA featured herein includes a sense sequence of a BCL11A dsRNA selected from the group consisting of SEQ ID NO:201, SEQ ID NO:257, SEQ ID NO:241, SEQ ID NO:239, SEQ ID NO:672 and SEQ ID NO:679; and an antisense sequence of a BCL11A dsRNA selected from the group consisting of SEQ ID NO:202, SEQ ID NO:258, SEQ ID NO:242, SEQ ID NO:240, SEQ ID NO:673 and SEQ ID NO:680. In certain embodiments, the BCL11A dsRNA has a modified sequence that includes a sense sequence of a BCL11A dsRNA selected from the group consisting of SEQ ID NO:293, SEQ ID NO:331, SEQ ID NO:329, SEQ ID NO:632 and SEQ ID NO:638; and an antisense sequence of a BCL11A dsRNA selected from the group consisting of SEQ ID NO:294, SEQ ID NO:332, SEQ ID NO:330, SEQ ID NO:633 and SEQ ID NO:639.

In one embodiment, an iRNA as described herein targets a wildtype KLF1 RNA or a wildtype BCL11A transcript variant, and in another embodiment, the iRNA targets a mutant transcript (e.g., a KLF1 RNA carrying an allelic variant). For example, an iRNA featured in the invention can target a polymorphic variant, such as a single nucleotide polymorphism (SNP), of KLF1 or BCL11A. In another embodiment, the iRNA targets both a wildtype and a mutant KLF1 or BCL11A transcript. In yet another embodiment, the iRNA targets a particular transcript variant of KLF1 or BCL11A (e.g., BCL11A variant 1, variant 2 or variant 3). In yet another embodiment, the iRNA agent targets multiple transcript vari-

5

ants (e.g., at least two or all three variants of BCL11A). For example, the iRNA agent targets each of variants 1, 2 and 3 of BCL11A. In another embodiment, the iRNA agent targets multiple transcript variants in multiple species. For example, the iRNA agent targets each of variants 1, 2 and 3 of BCL11A from human and from mouse.

In one embodiment, an iRNA featured in the invention targets a non-coding region of a KLF1 RNA transcript or BCL11A RNA variant transcript, such as the 5' or 3' untranslated region of a transcript.

In one aspect, the invention provides a cell containing at least one of the iRNAs featured in the invention. The cell is generally a mammalian cell, such as a human cell. In some embodiments, the cell is a hematopoietic cell, such as an erythroid cell (e.g., a red blood cell), or a progenitor cell thereof (e.g., an erythroid progenitor cell).

In another aspect, the invention provides a pharmaceutical composition for inhibiting the expression of a KLF1 gene or a BCL11A variant transcript in an organism, generally a human subject. The composition typically includes one or more of the iRNAs described herein and a pharmaceutically acceptable carrier or delivery vehicle. In one embodiment, the composition is used for treating a hemoglobinopathy, e.g., a sickle cell disease, such as a sickle cell disease.

In another embodiment, the pharmaceutical composition is formulated for administration of a dosage regimen described herein, e.g., not more than once every four weeks, not more than once every three weeks, not more than once every two weeks, or not more than once every week. In another embodiment, the administration of the pharmaceutical composition can be maintained for a month or longer, e.g., one, two, three, or six months, or one year or longer.

In another embodiment, a composition containing an iRNA featured in the invention, e.g., a dsRNA targeting KLF-1 or BCL11A, is administered with a non-iRNA therapeutic agent, such as an agent known to treat a hemoglobinopathy, or a symptom of a hemoglobinopathy. In another embodiment, a composition containing an iRNA featured in the invention, e.g., a dsRNA targeting KLF-1 or BCL11A, is administered along with a non-iRNA therapeutic regimen, such as a blood transfusion, or administration of hydroxyurea or erythropoietin. For example, an iRNA featured in the invention can be administered following a blood transfusion, and optionally also in combination with an iron chelator. In another example, an iRNA featured in the invention can be administered following a bone marrow transplant. The KLF-1 iRNA and BCL11A iRNA can be administered alone, or in combination, simultaneously or sequentially.

In one embodiment, a KLF1 or BCL11A iRNA is administered to a patient, and then the non-iRNA agent or therapeutic regimen is administered to the patient (or vice versa). In another embodiment, a KLF1 or BCL11A iRNA and the non-iRNA therapeutic agent or therapeutic regimen are administered at the same time.

In another aspect, the invention provides a method for reducing or inhibiting the expression of a KLF-1 or BCL11A gene, or a combination thereof, in a cell (e.g., a hematopoietic (e.g., an erythroid) cell, or a progenitor cell thereof). The method includes:

- (a) introducing into the cell a double-stranded ribonucleic acid (dsRNA), wherein the dsRNA includes at least two sequences that are complementary to each other. The dsRNA has a sense strand having a first sequence and an antisense strand having a second sequence; the antisense strand has a region of complementarity that is substantially complementary to at least a part of an mRNA encoding KLF1 or BCL11A, or a combination thereof,

6

and where the region of complementarity is 30 nucleotides or less, i.e., 15-30 nucleotides in length, and generally 19-24 nucleotides in length, and where the dsRNA individually or in combination, upon contact with a cell expressing KLF1 or BCL11A, inhibits expression of a KLF1 or BCL11A gene by at least 10%, e.g., at least 20%, at least 30%, at least 40% or more; and

- (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of the KLF1 or BCL11A gene, thereby reducing or inhibiting expression of a KLF1 or BCL11A gene in the cell.

In certain embodiments, the cell (e.g., the hematopoietic (e.g., an erythroid) progenitor cell) is a mammalian cell (e.g., of human, non-human primate, or rodent cell).

In one embodiment, the cell is treated ex vivo, in vitro, or in vivo (e.g., the cell is present in a subject (e.g., a patient in need of treatment, prevention and/or management of a hemoglobinopathy). In one embodiment, the subject is a mammal (e.g., a human) at risk, or diagnosed with a hemoglobinopathy, e.g., a  $\beta$ -hemoglobinopathy. In another embodiment, the hemoglobinopathy is a sickle cell disease. In another embodiment, the hemoglobinopathy is a sickle cell disease, including but not limited to, sickle cell anemia (SS), sickle-hemoglobin C disease (HbSC), sickle  $\beta^+$ -thalassemia (HbS/ $\beta^+$ ), SE disease, and sickle  $\beta^0$ -thalassemia (HbS/ $\beta^0$ ). In another embodiment, the hemoglobinopathy is  $\beta$ -thalassemia.

In one embodiment, the dsRNA introduced reduces or inhibits expression of a KLF1 or BCL11A gene, or a combination thereof, in the cell.

In one embodiment, the dsRNA introduced reduces or inhibits expression of a KLF1 gene by at least 10%, 20%, 30%, 40%, 50% or more compared to a reference value, e.g., an untreated cell. Without being bound by theory, KLF1 is a transcription factor that regulates the expression of BCL11A, a downstream target. Thus, reducing expression of the KLF1 gene is likely to reduce KLF1 protein, which in turn will lead to a decrease in the expression of BCL11A.

In other embodiments, the dsRNA introduced reduces or inhibits expression of a BCL11A gene by at least 10%, 20%, 30%, 40%, 50% or more compared to a reference value, e.g., an untreated cell.

In other embodiments, a combination of the dsRNA is introduced, wherein at least two of the dsRNA are substantially complementary to at least a part of an mRNA encoding KLF1 and BCL11A, thereby reducing or inhibiting the expression of each of a KLF1 gene and a BCL11A gene by at least 10%, 20%, 30%, 40%, 50% or more compared to a reference value, e.g., an untreated cell.

In other aspects, the invention provides methods for treating, preventing or managing pathological processes mediated by KLF1 or BCL11A expression. In one embodiment, the method includes administering to a subject, e.g., a patient in need of such treatment, prevention or management, an effective (e.g., a therapeutically or prophylactically effective) amount of one or more of the iRNAs featured in the invention. In one embodiment, the patient has a hemoglobinopathy. In another embodiment, administration of the iRNA targeting KLF1 or BCL11A alleviates or relieves the severity of at least one symptom of a KLF1- or BCL11A-mediated disorder in the patient.

In one embodiment, the patient is a mammal (e.g., a human) at risk, or that has been diagnosed with, a hemoglobinopathy. In a further embodiment, the hemoglobinopathy is a  $\beta$ -hemoglobinopathy. In another embodiment, the hemoglobinopathy is a sickle cell disease, including but not limited to, sickle cell anemia (SS), sickle-hemoglobin C disease

(HbSC), sickle  $\beta^+$ -thalassemia (HbS/ $\beta^+$ ), SE disease, and sickle  $\beta^0$ -thalassemia (HbS/ $\beta^0$ ). In another embodiment, the hemoglobinopathy is  $\beta$ -thalassemia.

In another aspect, the invention provides methods for increasing fetal hemoglobin levels in a cell (e.g., a hematopoietic (e.g., an erythroid) cell). The method includes contacting the cell with an effective amount of one or more of the iRNAs targeting KLF1 and/or BCL11A, e.g., one or more of the iRNAs disclosed herein, thereby increasing the expression of fetal hemoglobin in the cell, or its progeny, relative to the cell prior to contacting. In one embodiment, the increase in fetal hemoglobin levels is effected by one or more of delaying a fetal switch from fetal hemoglobin to adult hemoglobin, or by reactivating fetal hemoglobin (HbF) in the adult stage. Such methods can be used to treat (e.g., ameliorate the clinical severity) of  $\beta$ -hemoglobin disorders, such as sickle cell anemia and  $\beta$ -thalassemias.

In another aspect, the invention provides methods for decreasing  $\beta$ -globin levels in a cell (e.g., a hematopoietic (e.g., an erythroid) cell). The method includes contacting the cell with one or more of the iRNAs targeting KLF1, e.g., one or more of the iRNAs disclosed herein, in an amount effective to reduce expression of KLF1, thereby decreasing the expression of  $\beta$ -globin in the cell, or its progeny, relative to the cell prior to contacting. In one embodiment, the  $\beta$ -globin has an abnormality in structure or function, e.g., a point mutation in a  $\beta$ -globin structural gene that leads to the production of an abnormal (sickled) hemoglobin (HbS) in Sickle cell anemia.

In one embodiment, the contacting step is effected ex vivo, in vitro, or in vivo. For example, the cell can be present in a subject, e.g., a mammal (e.g., a human) at risk, or that has been diagnosed with, a hemoglobinopathy. In a further embodiment, the hemoglobinopathy is a  $\beta$ -hemoglobinopathy. In another embodiment, the hemoglobinopathy is a sickle cell disease, including but not limited to, sickle cell anemia (SS), sickle-hemoglobin C disease (HbSC), sickle  $\beta^+$ -thalassemia (HbS/ $\beta^+$ ), SE disease, and sickle  $\beta^0$ -thalassemia (HbS/ $\beta^0$ ). In another embodiment, the hemoglobinopathy is  $\beta$ -thalassemia.

In a further embodiment, the cell is a hematopoietic (e.g., an erythroid) cell. For example, the cell can be a progenitor cell of the erythroid lineage.

In one aspect, the invention provides a vector for inhibiting the expression of a KLF1 gene or a BCL11A gene in a cell. In one embodiment, the vector includes at least one regulatory sequence operably linked to a nucleotide sequence that encodes at least one strand of an iRNA as described herein. In one embodiment the vector comprises at least one strand of a KLF1 iRNA, and in another embodiment, the vector comprises at least one strand of a BCL11A iRNA. In another embodiment, the vector comprises at least one strand of a KLF1 iRNA and at least one strand of a BCL11A iRNA. In one embodiment, the vector comprising at least one strand of a KLF1 iRNA and at least one strand of a BCL11A iRNA further comprises a regulatory sequence that regulates expression of the at least one strand of a KLF1 iRNA and at least one strand of a BCL11A iRNA. In another embodiment, the vector comprising at least one strand of a KLF1 iRNA and at least one strand of a BCL11A iRNA comprises a first regulatory sequence that regulates expression of the at least one strand of a KLF1 iRNA and a second regulatory sequence that regulates expression of the at least one strand of a BCL11A iRNA.

In another aspect, the invention provides a cell containing a vector for inhibiting the expression of a KLF1 or a BCL11A gene in a cell. The vector includes a regulatory sequence operably linked to a nucleotide sequence that encodes at least

one strand of one of the iRNAs as described herein. In one embodiment, the cell is a hematopoietic (e.g., an erythroid) cell. For example, the cell can be a progenitor cell of the erythroid lineage.

In yet another aspect, the invention provides a composition containing a KLF1 iRNA, in combination with a BCL11A iRNA, and further in combination with a third iRNA targeting a third gene involved in a pathological disease, and useful for treating the disease, e.g., a hemoglobinopathy.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The details of various embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

## DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the sequence of human KLF1 mRNA (Ref. Seq. NM\_006563.3, SEQ ID NO: 1).

FIG. 2 depicts the sequence of mouse KLF1 mRNA (Ref. Seq. NM\_010635.2 (GI:225543579), SEQ ID NO: 2).

FIGS. 3A-3C depict the sequence of human BCL11A variant 1 mRNA (Ref. Seq. NM\_022893.3 (GI:148539885), SEQ ID NO: 3).

FIGS. 4A-4B depict the sequence of human BCL11A variant 2 mRNA (Ref. Seq. NM\_018014.3 (GI:148539884), SEQ ID NO: 4).

FIGS. 5A-5B depict the sequence of human BCL11A variant 3 mRNA (Ref. Seq. NM\_138559.1 (GI:20336312), SEQ ID NO: 5).

FIGS. 6A-6B depict the sequence of mouse BCL11A variant 1 mRNA (Ref. Seq. NM\_016707.3 (GI:226530130), SEQ ID NO: 6).

FIG. 7 depicts the sequence of mouse BCL11A variant 2 mRNA (Ref. Seq. NM\_001159289.1 (GI:22653015.1), SEQ ID NO: 7).

FIG. 8 depicts the sequence of mouse BCL11A variant 3 mRNA (Ref. Seq. NM\_001159290.1 (GI:226530196), SEQ ID NO: 8).

FIGS. 9A-9D depict the IC<sub>50</sub> plots of select BCL11a siRNA duplexes in in vitro screens. FIGS. 9A-9B depict the IC<sub>50</sub> plots of select BCL11a siRNA duplexes, with silencing of BCL11a activity expressed as the fraction mRNA message remaining relative to the negative control siRNA AD-1955. FIGS. 9C-9D depict the IC<sub>50</sub> plots of select BCL11a siRNA duplexes, with silencing of BCL11a activity expressed as the fraction mRNA message remaining relative to that of the lowest tested siRNA dose.

FIGS. 10A and 10B depict the increased expression of mouse embryonic hemoglobin post BCL11a siRNA mediated knockdown of BCL11a in a murine erythroleukemic cell line. FIG. 10A depicts the dose dependent knockdown of BCL11a expression 24 hours post transfection with BCL11a siRNA (using LNP-009, also referred to herein as "AF-009"). FIG. 10B depicts the increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$  and  $\beta\text{h}1$  measured 72 hours post transfection with BCL11a siRNA (using LNP-012, also referred to herein as "AF-012").

FIGS. 11A and 11B depict the increased expression of mouse embryonic hemoglobin post BCL11a siRNA mediated knockdown of BCL11a in murine bone marrow progenitor cells. FIG. 11A depicts the knockdown of BCL11a expression 72 and 96 hours post transfection with BCL11a siRNA. FIG. 11B depicts the increased expression of the mouse

embryonic hemoglobin gene  $\epsilon\gamma$  measured at both 72 and 96 hours post siRNA transfection.

FIGS. 12A-12C depict the detection of mouse hemoglobin switching in vivo. FIG. 12A depicts the detection of mouse adult hemoglobin  $\beta$ maj at the E16 developmental stage, and subsequent developmental time points, including E18, as well as in the bone marrow; but no significant expression in the E12 developmental stage. FIG. 12B depicts the detection of mouse embryonic hemoglobin  $\epsilon\gamma$  only in the E12 developmental stage, and in no subsequent developmental stages or in the bone marrow. FIG. 12C depicts the detection of mouse embryonic hemoglobin  $\beta$ h1 also only in the E12 developmental stage, and not in the bone marrow or spleen.

FIGS. 13A and 13B depict increased expression of mouse embryonic hemoglobin post KLF1 siRNA mediated knockdown of KLF1 in a murine erythroleukemic cell line. FIG. 13A depicts the dose dependent knockdown of KLF1 expression 24 hours post transfection with KLF1 siRNA (encapsulated in AF-009). FIG. 13B depicts the increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$  and  $\beta$ h1 measured 72 hours post transfection with KLF1 siRNA (encapsulated in AF-009).

FIGS. 14A-14E depict the selective inhibition of mKLF1 mRNA in the bone marrow and spleen, and increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$ , using mKLF1 iRNA at a concentration of  $3 \times 1$  mg/kg encapsulated in AF-012. A 95% reduction of mKLF1, normalized to GAPDH loading control, was detected in the treated bone marrow; a 75% reduction of mKLF1, normalized to GAPDH loading control, was detected in the treated spleen. Increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$  in bone marrow (FIG. 14B) and spleen (FIG. 14D) is detected after treatment with mKLF1 iRNA. FIG. 14E depicts a diagram of the mouse hemoglobin genes.

#### DETAILED DESCRIPTION OF THE INVENTION

Described herein are iRNAs and methods of using them for inhibiting the expression of a KLF1 gene and/or BCL11A gene in a cell or a mammal where the iRNA targets a KLF1 gene and/or BCL11A gene. Also provided are compositions and methods for treating pathological conditions and diseases, such as hemoglobinopathies (e.g.,  $\beta$ -hemoglobinopathies, sickle cell disease (SCD) and the  $\beta$ -thalassemias), in a mammal caused by or modulated by the expression of a KLF1 gene and/or BCL11A gene. iRNA directs the sequence-specific degradation of mRNA through a process known as RNA interference (RNAi).

The human  $\beta$ -globin locus contains the linked embryonic ( $\epsilon$ ), fetal ( $\gamma$  and  $\delta$ ), and adult ( $\delta$  and  $\beta$ ) globin genes. These genes are expressed sequentially during development. Fetal hemoglobin (HbF) is a tetramer of two adult  $\alpha$ -globin polypeptides and two fetal  $\beta$ -like  $\gamma$ -globin polypeptides. During gestation, the duplicated  $\gamma$ -globin genes constitute the predominant genes transcribed from the  $\beta$ -globin locus. Following birth,  $\gamma$ -globin becomes progressively replaced by adult  $\beta$ -globin, a process referred to as the "fetal switch." The developmental switch from production of predominantly fetal hemoglobin or HbF ( $\alpha_2\gamma_2$ ) to production of adult hemoglobin or HbA ( $\alpha_2\beta_2$ ) begins at about 28 to 34 weeks of gestation and continues shortly after birth at which point HbA becomes predominant. This switch results primarily from decreased transcription of the  $\gamma$ -globin genes and increased transcription of  $\beta$ -globin genes. This switch is of particular clinical relevance.

Hemoglobinopathies encompass a number of anemias of genetic origin in which there is a decreased production and/or

increased destruction (hemolysis) of red blood cells (RBCs). These disorders also include genetic defects that result in the production of abnormal hemoglobins with a concomitant impaired ability to maintain oxygen concentration. Some such disorders involve the failure to produce normal  $\beta$ -globin in sufficient amounts, while others involve the failure to produce normal  $\beta$ -globin entirely. These disorders specifically associated with the  $\beta$ -globin protein are referred to generally as  $\beta$ -hemoglobinopathies. For example,  $\beta$ -thalassemias result from a partial or complete defect in the expression of the  $\beta$ -globin gene, leading to an imbalance of the  $\alpha$  and  $\beta$  chains of Hb.  $\beta$ -thalassemias result from mutations with either non-expressing ( $\beta^0$ ) or low expressing ( $\beta^+$ ) alleles in chromosome 11. The clinical severity correlates with the allele deficiencies. For example, normal individuals have a  $\beta/\beta$  genotype; individuals with minor or trait  $\beta$ -thalassemia have a  $\beta/\beta^0$  or  $\beta/\beta^+$  genotype;  $\beta$ -thalassemia intermedia individuals have a  $\beta^0/\beta^+$ ; and  $\beta$ -thalassemia major phenotypes have a  $\beta^0/\beta^0$  or  $\beta^+/ \beta^+$  genotype (reviewed in Muncie and Campbell (2009) *AM J Phys.* 80(4):339-344). The clinical features of  $\beta$ -thalassemia major can be detected between 6-24 months of age with failure to thrive. Additional symptoms include hemolysis (e.g., anemia and splenomegaly); ineffective erythropoiesis (e.g., bone marrow drive (skeletal changes), hepato-splenomegaly, consumption of haematinics, and high uric acid in blood); infections; and leg ulcers. Complications of treatment include iron overload (endocrinopathy, liver fibrosis and cardiac fibrosis). Therapeutic modalities for the management of  $\beta$ -thalassemia major include red cell transfusions, iron chelation, antibiotics, antivirals, and stem cell or bone marrow transplants. Other modalities under investigation include treatment with hydroxyurea, butyric acid, HbF inducing agents and gene therapy.

Sickle cell anemia results from a point mutation in the  $\beta$ -globin structural gene, leading to the production of an abnormal (sickled) hemoglobin (HbS). HbS RBCs are more fragile than normal RBCs and undergo hemolysis more readily, leading eventually to anemia (Atweh (2001), *Semin. Hematol.* 38(4):367-73). The clinical features of sickle cell disease (SCD) include hemolysis (e.g., anemia, jaundice, cholelithiasis, aplastic crisis and hemolytic crisis) and vaso-occlusive disease (e.g., dactylitis, autosplenectomy, acute chest syndrome, stroke, priapism, renal papillary necrosis, infarctive or sequestration crisis, and leg ulcers, among others). Therapeutic modalities for the management of SCD include treatment with hydroxyurea (hydroxycarbamide), red cell transfusions, iron chelation, antibiotics and stem cell or bone marrow transplants.

Therapeutic approaches aimed at reducing globin chain imbalance in patients with  $\beta$ -hemoglobinopathies have focused on the pharmacologic manipulation of fetal hemoglobin ( $\alpha_2\gamma_2$ ; HbF). The upstream  $\gamma$  globin genes are frequently intact and fully functional in the majority of patients with  $\beta$ -hemoglobinopathies. Thus, delaying the switch or reactivating fetal hemoglobin (HbF) in the adult stage has been shown to ameliorate the clinical severity of  $\beta$ -hemoglobin disorders, such as sickle cell anemia and  $\beta$ -thalassemias (Atweh, (2001) *Semin. Hematol.* 38(4):367-73). The therapeutic potential of such approaches is suggested by the fact that SCD symptoms are not evident until infancy or childhood, which correlated with a reduction in the levels of HbF (e.g., HbF is typically less than 5% total Hb at 6 months, whereas it is less than 1% at 2 years). In addition, natural HbF levels correlate with the level of morbidity in response to cerebrovascular accidents. For example, there is approximately a 5-fold decrease in frequency of cerebrovascular accidents in patients with greater than 10% levels of HbF, as

opposed to patients who have lower levels of HbF (Powars et al. (1984) *Blood* 63:921-926). Furthermore, observations of the mild phenotype of individuals with co-inheritance of both homozygous  $\beta$ -thalassemia and hereditary persistence of fetal hemoglobin (HPFH), as well as by those patients with homozygous  $\beta^0$ -thalassemia who synthesize no adult hemoglobin, but in whom a reduced requirement for transfusions is observed in the presence of increased concentrations of fetal hemoglobin. Multiple publications establish a link between HbF levels and  $\beta$ -thalassemia severity (reviewed in, for example, Thein et al. (2009) *Hum Mol Gen Br J Haematol* 145: 455-467). Therapeutic augmentation of HbF in hydroxyurea-treated SCD patients compared to untreated patients leads to a lower rate of crisis (e.g., 2.5 vs 4.5 crises per year) (Charache et al. (1995) *NEJM* 332(20):1317-22). In addition, certain populations of adult patients with  $\beta$  chain abnormalities have higher than normal levels of fetal hemoglobin (HbF); these patients have been observed to have a milder clinical course of disease than patients with normal adult levels of HbF. Moreover, therapeutic trials have shown conversion to transfusion independence with HbF-inducing agents in  $\beta$ -thalassemia major or intermedia (Perrine, S. P. (2005) *Hematology* 1: 37-44). In patients with adult hemoglobin disorders increased levels of HbF can reduce disease severity, morbidity and mortality (reviewed in *Br. J. Haematol.* 102: 415-422 (1998) and Bunn, N. *Engl. J. Med.* 328: 129-131 (1993)). Thus,  $\beta$ -hemoglobinopathies, such as sickle cell anemia and the  $\beta$ -thalassemias, can be ameliorated by increased HbF levels.

Recent human genetic studies focused on natural variation in the level of HbF expression in human populations has shed some light on the developmental control of hemoglobin switching and silencing of  $\gamma$ -globin expression (Thein and Menzel (2009) *Br J Haematol.* 145:455-467; Thein et al. (2009) *Hum Mol Genet* 18:R216-R233). The gene BCL11A encodes a zinc finger transcription factor; knockdown of BCL11A enhances HbF expression in human erythroid progenitors (Sankaran et al. (2008) *Science* 322: 1839-1842). BCL11A modulation is able to modify the phenotype of homozygous  $\beta$ -thalassemia by augmenting HbF levels in Sardinian population (Uda et al. (2008) *PNAS* 105(5):1620-5). BCL11A accounts for approximately 15% of HbF variability in Northern Europeans (Menzel et al. (2007) *Nat. Gen.* 39, 1197-1199). Alternative names for BCL11A include B-cell CLL/lymphoma 11A; B-cell lymphoma/leukemia 11A; BCL-11A; BCL11A-L, -XL, and -S; COUP-TF-interacting protein 1; CTIP1; HBFQTL5; KIAA1809; Ecotropic viral integration site 9 protein homolog; EVI9; EVI-9; FLJ34997; C2H2-type zinc finger protein; Zinc finger protein 856; and ZNF856. BCL11a is expressed in fetal brain, germinal center cells, erythroid cells, bone marrow and fetal liver leukocyte precursors. BCL11a functions as a myeloid and B-cell proto-oncogene. Mice deficient in BCL11a produce myeloid and erythroid cells, but show undetectable B cells and thymocyte maturation. The mRNA sequences of three variants of human BCL11A are provided in FIGS. 3, 4, 5, 6 and 7, respectively, and the mRNA sequences of three variants of mouse BCL11A are provided in FIGS. 6, 7, and 8, respectively.

Abundant expression of full length forms of BCL11A is developmentally restricted to adult erythroid cells (Sankaran et al. (2008) supra; Sankaran et al. (2009) *Nature* 460:1093-1097). Downregulation of BCL11A expression in adult human erythroid precursors leads to robust induction of HbF (Sankaran et al. (2008) supra). Knock-out of BCL11A in transgenic mice harboring the human  $\beta$ -globin locus prevents proper silencing of endogenous mouse  $\beta$ -like embryonic genes and human  $\gamma$ -globin genes in adult erythroid cells of the

fetal liver (Sankaran et al. (2009) supra). Moreover, the presence of a BCL11A genetic variant ameliorates the clinical severity in  $\beta$ -thalassemia. This variant has been shown to be associated with HbF levels. Thus, the BCL11A transcription factor is a negative regulator of  $\gamma$ -globin expression. Inhibition of BCL11A gene expression or activity can be a useful approach to therapies aimed at increasing HbF production, such as treatment of  $\beta$ -hemoglobinopathies, such as sickle cell anemia and the  $\beta$ -thalassemias.

Expression of BCL11A is regulated by KLF1 (also known as Erythroid Krueppel-like transcription factor (EKLF), INLU, Krueppel-like factor 1, or Kruppel-like factor 1). KLF1 is a zinc-finger transcription factor that is expressed in erythroid cells and positively regulates the adult  $\beta$ -globin gene (Miller, I. J. et al. (1993) *Mol Cell Biol* 13:2776-2786; Donze, D. et al. (1995) *J Biol. Chem.* 270:1955-1959). KLF1 is an erythroid-specific transcription factor that induces high level expression of adult  $\beta$ -globin, induces BCL11a (which silences  $\gamma$ -globin) and other erythroid genes. KLF1+/- individuals typically have lower levels of BCL11a, higher HbF, and are generally healthy (Borg et al. (2010) *Nat. Genetics* 43: 295-301). The mRNA sequence of human KLF1 mRNA is provided in FIG. 1. The mRNA sequence of mouse KLF1 mRNA is provided in FIG. 2.

KLF1 plays an important role in hemoglobin metabolism and membrane stability in primitive erythroid cells. KLF1 is also an important activator of BCL11A, which encodes a suppressor of fetal hemoglobin. Knockdown of KLF1 in human and mouse adult erythroid progenitors markedly reduced BCL11A levels and increased human  $\beta$ -globin/ $\beta$ -globin expression ratios (Zhou et al. (2010) *Nat. Genet.* 42:742-744). Loss-of-function mutations in the KLF1 gene have been associated with hereditary persistence of fetal hemoglobin (HPFH), which is characterized by persistent high levels of HbF in adults (Borg et al. (2010) supra).

Thus, KLF1 upregulates expression of BCL11A in erythroid cells. BCL11A expression, in turn, represses  $\gamma$ -globin expression, thus leading to low  $\gamma$  (fetal) globin levels relative to  $\beta$  (adult) globin levels. In certain embodiments, inhibition of KLF1 is expected to decrease expression of the adult  $\beta$ -globin gene. Alternatively, or in combination, inhibition of KLF1 is expected to decrease expression of BCL11A, thus leading to higher levels of  $\gamma$  (fetal) globin relative to  $\beta$  globin levels. In certain embodiments, other targets can be considered in addition to induction of HbF, for example, suppression of hemoglobin  $\alpha$ . Accordingly, inhibition of KLF1 gene expression or activity, e.g., in erythroid precursors (e.g., adult erythroid precursors) can be a useful approach to therapies aimed at decreasing KLF1, and/or increasing HbF production. Additional targets that can be inhibited (e.g., by partial silencing), along or in combination with a KLF1 gene and/or a BCL11A gene include Myb, Sox6 and/or COUP-TFII genes. Such inhibition can be useful in treating  $\beta$ -hemoglobinopathies, such as sickle cell anemia and the  $\beta$ -thalassemias.

The present invention describes methods and iRNA compositions for modulating the expression of a KLF1 gene and/or a BCL11A gene. In certain embodiments, expression of KLF1 is reduced or inhibited using a KLF-specific iRNA, thereby leading to a decreased expression of adult  $\beta$ -globin genes. Reduced expression of KLF1 gene can also negatively regulate expression of BCL11A, thus leading to higher levels of  $\gamma$  (fetal) globin relative to  $\beta$  globin levels. Alternatively, or in combination with inhibition of KLF1 gene expression, expression of BCL11A can be reduced or inhibited using a BCL11A-specific iRNA, thereby causing higher levels of  $\gamma$  (fetal) globin relative to  $\beta$  globin levels. Thus, inhibition of

KLF1 and/or a BCL11A gene expression or activity using the iRNA compositions featured in the invention can be a useful approach to therapies aimed at reducing the expression of adult  $\beta$ -globin genes, and/or increasing fetal hemoglobin (HbF) production. Such inhibition can be useful in treating hemoglobinopathies, such as  $\beta$ -hemoglobinopathies, sickle cell disease and the  $\beta$ -thalassemias.

The iRNAs of the compositions featured herein include an RNA strand (the antisense strand) having a region which is 30 nucleotides or less in length, i.e., 15-30 nucleotides in length, generally 19-24 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a KLF1 gene or a BCL11A gene (also referred to herein as a "KLF1-specific iRNA" and a "BCL11A-specific iRNA," respectively). The use of these iRNAs enables the targeted degradation of mRNAs of genes that are implicated in pathologies associated with KLF1 and BCL11A expression in mammals, e.g., hemoglobinopathies. Very low dosages of KLF1-specific iRNAs and/or BCL11A-specific iRNAs can specifically and efficiently mediate RNAi, resulting in significant inhibition of expression of a KLF1 and/or BCL11A gene. iRNAs targeting KLF1 or BCL11A can specifically and efficiently mediate RNAi, resulting in significant inhibition of expression of a KLF1 or BCL11A gene, e.g., in cell based assays. Thus, methods and compositions including these iRNAs are useful for treating pathological processes that can be mediated by down regulating KLF1 and/or BCL11A, such as hemoglobinopathies, including but not limited to, sickle cell anemia (SS), sickle-hemoglobin C disease (HbSC),  $\beta$ -thalassemia, SE disease, and sickle  $\beta^0$ -thalassemia (HbS/ $\beta^0$ ).

The following description discloses how to make and use compositions containing iRNAs to inhibit the expression of a KLF1 and/or BCL11A gene, as well as compositions and methods for treating diseases and disorders caused by or modulated by the expression of this gene. Embodiments of the pharmaceutical compositions featured in the invention include an iRNA having an antisense strand comprising a region which is 30 nucleotides or less in length, generally 19-24 nucleotides in length, which region is substantially complementary to at least part of an RNA transcript of a KLF1 gene or BCL11A gene, together with a pharmaceutically acceptable carrier. Embodiments of compositions featured in the invention also include an iRNA having an antisense strand having a region of complementarity which is 30 nucleotides or less in length, generally 19-24 nucleotides in length, and is substantially complementary to at least part of an RNA transcript of a KLF1 gene or BCL11A gene.

Accordingly, in some aspects, pharmaceutical compositions containing a KLF1 gene and/or BCL11A iRNA and a pharmaceutically acceptable carrier, methods of using the compositions to inhibit expression of a KLF1 gene and/or BCL11A gene, and methods of using the pharmaceutical compositions to treat diseases caused by expression of a KLF1 gene and/or BCL11A gene are featured in the invention.

#### I. Definitions

For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in other parts of this specification and its definition provided in this section, the definition in this section shall prevail.

"G," "C," "A," "T" and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine and uracil as a base, respectively. However, it will be understood that the term "ribonucleotide" or "nucleotide" can

also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety. The skilled person is well aware that guanine, cytosine, adenine, and uracil may be replaced by other moieties without substantially altering the base pairing properties of an oligonucleotide comprising a nucleotide bearing such replacement moiety. For example, without limitation, a nucleotide comprising inosine as its base may base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine may be replaced in the nucleotide sequences of dsRNA featured in the invention by a nucleotide containing, for example, inosine. In another example, adenine and cytosine anywhere in the oligonucleotide can be replaced with guanine and uracil, respectively to form G-U Wobble base pairing with the target mRNA. Sequences containing such replacement moieties are suitable for the compositions and methods featured in the invention.

As used herein, "BCL11A" (also known as Evi9, Ct1p1, B-cell CLL/lymphoma 11A (zinc finger protein); BCL11A-L, -XL, and -S; COUP-TF-interacting protein 1; CTIP1; HBFQTL5; KIAA1809; Ecotropic viral integration site 9 protein homolog; EVI9; EVI-9; C2H2-type zinc finger protein) refers to a transcription factor that is predominantly expressed in erythroid cells. As used herein "BCL11A protein" means any protein variant of BCL11A (including, e.g., variants 1, 2, 3), from any species (e.g., mouse, human non-human primate), as well as any mutants, and fragments thereof that retain a BCL11A activity. Similarly, a "BCL11A transcript" refers to any transcript variant of BCL11A, e.g., variant 1, 2, or 3, from any species, e.g., mouse, human, or non-human primate. The sequence of human BCL11A variant 1 mRNA transcript can be found at NM\_022893.3 (FIG. 3; SEQ ID NO: 3). The sequence of human BCL11A variant 2 mRNA transcript can be found at NM\_018014.3 (FIG. 4; SEQ ID NO: 4). The sequence of human BCL11A variant 3 mRNA transcript can be found at NM\_138559.1 (FIG. 5; SEQ ID NO: 5). The sequence of mouse BCL11A variant 1 mRNA transcript can be found at NM\_016707.3 (GI:226530130) (FIG. 6; SEQ ID NO: 6). The sequence of mouse BCL11A variant 2 mRNA transcript can be found at NM\_001159289.1 (GI:226530151) (FIG. 7; SEQ ID NO: 7). The sequence of mouse BCL11A variant 3 mRNA transcript can be found at NM\_001159290.1 (GI:226530196) (FIG. 8; SEQ ID NO: 8).

The amino acid sequence of BCL11a variant 2 (SEQ ID NO: 4) differs from the canonical sequence (SEQ ID NO: 3) as follows: amino acids 745-773 of the canonical sequence (SEQ ID NO.: 3): EYCGKVFKNCSNLTVHRRSHTGERPYKCE (SEQ ID NO.: 622); are replaced with amino acids SSHTPIRRSTQRAQDVWQFSDGSSRALKF (SEQ ID NO: 623); and amino acids 774-835 of the canonical sequence (SEQ ID NO: 3) are missing. The amino acid sequence of BCL11a variant 3 (SEQ ID NO: 5) differs from the canonical sequence (SEQ ID NO: 3) as follows: amino acids 212-243 of the canonical sequence (SEQ ID NO: 3): GIPSGLGAECPSQPPLHGIHIADNNPFNLLRI (SEQ ID NO: 624) are replaced with amino acids LHPTPFGVVPRELKMCGRMEAREPLSSEKI (SEQ ID NO: 625); and amino acids 244-835 are not present.

In one embodiment, the iRNA comprises a stand that is complementary to exon 4 of BCL11a, e.g., human BCL11a. BCL11a variant 2 (NM\_018014.3; SEQ ID NO.: 4) is characterized by a long form of exon 4. Exemplary exon 4 sequences of BCL11a variants 1, 2 and 3, include Exon 4 of BCL11a variant 2 (SEQ ID NO.: 4) corresponds to nucleotides 716-2458 of SEQ ID NO:4 depicted in FIG. 4A-4B; Exon 4 of BCL11a variant 1 (NM\_022893.3; SEQ ID NO: 3)

corresponds to nucleotides 716-5946 of SEQ ID NO: 3 depicted in FIG. 3A-3C; and Exon 4 of BCL11a variant 3 (NM\_138559; SEQ ID NO.: 5) corresponds to nucleotides 716-858 of SEQ ID NO: 5; depicted in FIG. 5A-5B.

As used herein, "Krueppel-like factor 1" or "KLF1" (also known as Erythroid krueppel-like transcription factor (EKLF), Kruppel-like factor 1, INLU, and HBFQTL6) refers to a transcription factor that is predominantly expressed in erythroid cells. As used herein "KLF1 protein" means any protein variant of KLF1 from any species (e.g., mouse, human non-human primate), as well as any mutants and fragments thereof that retain a KLF1 activity. Similarly, a "KLF1 transcript" refers to any transcript of KLF1, e.g., from any species, e.g., mouse, human, or non-human primate. The sequence of human KLF1 mRNA transcript can be found at NM\_006563.3 (FIG. 1; SEQ ID NO: 1). The sequence of mouse KLF1 mRNA transcript can be found at NM\_010635.2 (FIG. 2; SEQ ID NO: 2).

As used herein, the term "iRNA" refers to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. In one embodiment, an iRNA as described herein effects inhibition of KLF1 expression. In another embodiment, an iRNA as described herein effects inhibition of BCL11A expression.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a BCL11A gene or a KLF1 gene, including mRNA that is a product of RNA processing of a primary transcription product. The target portion of the sequence will be at least long enough to serve as a substrate for iRNA-directed cleavage at or near that portion. For example, the target sequence will generally be from 9-36 nucleotides in length, e.g., 15-30 nucleotides in length, including all sub-ranges therebetween. As non-limiting examples, the target sequence can be from 15-30 nucleotides, 15-26 nucleotides, 15-23 nucleotides, 15-22 nucleotides, 15-21 nucleotides, 15-20 nucleotides, 15-19 nucleotides, 15-18 nucleotides, 15-17 nucleotides, 18-30 nucleotides, 18-26 nucleotides, 18-23 nucleotides, 18-22 nucleotides, 18-21 nucleotides, 18-20 nucleotides, 19-30 nucleotides, 19-26 nucleotides, 19-23 nucleotides, 19-22 nucleotides, 19-21 nucleotides, 19-20 nucleotides, 20-30 nucleotides, 20-26 nucleotides, 20-25 nucleotides, 20-24 nucleotides, 20-23 nucleotides, 20-22 nucleotides, 20-21 nucleotides, 21-30 nucleotides, 21-26 nucleotides, 21-25 nucleotides, 21-24 nucleotides, 21-23 nucleotides, or 21-22 nucleotides.

As used herein, the term "strand comprising a sequence" refers to an oligonucleotide comprising a chain of nucleotides that is described by the sequence referred to using the standard nucleotide nomenclature.

As used herein, and unless otherwise indicated, the term "complementary," when used to describe a first nucleotide sequence in relation to a second nucleotide sequence, refers to the ability of an oligonucleotide or polynucleotide comprising the first nucleotide sequence to hybridize and form a duplex structure under certain conditions with an oligonucleotide or polynucleotide comprising the second nucleotide sequence, as will be understood by the skilled person. Such conditions can, for example, be stringent conditions, where stringent conditions may include: 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50° C. or 70° C. for 12-16 hours followed by washing. Other conditions, such as physiologically relevant conditions as may be encountered inside an organism, can apply. The skilled person will be able to determine the set of conditions most appropriate for a test of

complementarity of two sequences in accordance with the ultimate application of the hybridized nucleotides.

Complementary sequences within an iRNA, e.g., within a dsRNA as described herein, include base-pairing of the oligonucleotide or polynucleotide comprising a first nucleotide sequence to an oligonucleotide or polynucleotide comprising a second nucleotide sequence over the entire length of one or both nucleotide sequences. Such sequences can be referred to as "fully complementary" with respect to each other herein. However, where a first sequence is referred to as "substantially complementary" with respect to a second sequence herein, the two sequences can be fully complementary, or they may form one or more, but generally not more than 5, 4, 3 or 2 mismatched base pairs upon hybridization for a duplex up to 30 base pairs, while retaining the ability to hybridize under the conditions most relevant to their ultimate application, e.g., inhibition of gene expression via a RISC pathway. However, where two oligonucleotides are designed to form, upon hybridization, one or more single stranded overhangs, such overhangs shall not be regarded as mismatches with regard to the determination of complementarity. For example, a dsRNA comprising one oligonucleotide 21 nucleotides in length and another oligonucleotide 23 nucleotides in length, wherein the longer oligonucleotide comprises a sequence of 21 nucleotides that is fully complementary to the shorter oligonucleotide, may yet be referred to as "fully complementary" for the purposes described herein.

"Complementary" sequences, as used herein, may also include, or be formed entirely from, non-Watson-Crick base pairs and/or base pairs formed from non-natural and modified nucleotides, in as far as the above requirements with respect to their ability to hybridize are fulfilled. Such non-Watson-Crick base pairs includes, but are not limited to, G:U Wobble or Hoogsteen base pairing.

The terms "complementary," "fully complementary" and "substantially complementary" herein may be used with respect to the base matching between the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an iRNA agent and a target sequence, as will be understood from the context of their use.

As used herein, a polynucleotide that is "substantially complementary to at least part of" a messenger RNA (mRNA) refers to a polynucleotide that is substantially complementary to a contiguous portion of the mRNA of interest (e.g., an mRNA encoding KLF1 or BCL11A). For example, a polynucleotide is complementary to at least a part of a KLF1 mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding KLF1. As another example, a polynucleotide is complementary to at least a part of a BCL11A mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding BCL11A.

The term "double-stranded RNA" or "dsRNA," as used herein, refers to an iRNA that includes an RNA molecule or complex of molecules having a hybridized duplex region that comprises two anti-parallel and substantially complementary nucleic acid strands, which will be referred to as having "sense" and "antisense" orientations with respect to a target RNA. The duplex region can be of any length that permits specific degradation of a desired target RNA through a RISC pathway, but will typically range from 9 to 36 base pairs in length, e.g., 15-30 base pairs in length. Considering a duplex between 9 and 36 base pairs, the duplex can be any length in this range, for example, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 and any sub-range therein between, including, but not limited to 15-30 base pairs, 15-26 base pairs, 15-23 base

pairs, 15-22 base pairs, 15-21 base pairs, 15-20 base pairs, 15-19 base pairs, 15-18 base pairs, 15-17 base pairs, 18-30 base pairs, 18-26 base pairs, 18-23 base pairs, 18-22 base pairs, 18-21 base pairs, 18-20 base pairs, 19-30 base pairs, 19-26 base pairs, 19-23 base pairs, 19-22 base pairs, 19-21 base pairs, 19-20 base pairs, 20-30 base pairs, 20-26 base pairs, 20-25 base pairs, 20-24 base pairs, 20-23 base pairs, 20-22 base pairs, 20-21 base pairs, 21-30 base pairs, 21-26 base pairs, 21-25 base pairs, 21-24 base pairs, 21-23 base pairs, or 21-22 base pairs. dsRNAs generated in the cell by processing with Dicer and similar enzymes are generally in the range of 19-22 base pairs in length. One strand of the duplex region of a dsDNA comprises a sequence that is substantially complementary to a region of a target RNA. The two strands forming the duplex structure can be from a single RNA molecule having at least one self-complementary region, or can be formed from two or more separate RNA molecules. Where the duplex region is formed from two strands of a single molecule, the molecule can have a duplex region separated by a single stranded chain of nucleotides (herein referred to as a "hairpin loop") between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure. The hairpin loop can comprise at least one unpaired nucleotide; in some embodiments the hairpin loop can comprise at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 20, at least 23 or more unpaired nucleotides. Where the two substantially complementary strands of a dsRNA are comprised by separate RNA molecules, those molecules need not, but can be covalently connected. Where the two strands are connected covalently by means other than a hairpin loop, the connecting structure is referred to as a "linker." The term "siRNA" is also used herein to refer to a dsRNA as described above.

The skilled artisan will recognize that the term "RNA molecule" or "ribonucleic acid molecule" encompasses not only RNA molecules as expressed or found in nature, but also analogs and derivatives of RNA comprising one or more ribonucleotide/ribonucleoside analogs or derivatives as described herein or as known in the art. Strictly speaking, a "ribonucleoside" includes a nucleoside base and a ribose sugar, and a "ribonucleotide" is a ribonucleoside with one, two or three phosphate moieties. However, the terms "ribonucleoside" and "ribonucleotide" can be considered to be equivalent as used herein. The RNA can be modified in the nucleobase structure or in the ribose-phosphate backbone structure, e.g., as described herein below. However, the molecules comprising ribonucleoside analogs or derivatives must retain the ability to form a duplex. As non-limiting examples, an RNA molecule can also include at least one modified ribonucleoside including but not limited to a 2'-O-methyl modified nucleotides, a nucleoside comprising a 5' phosphorothioate group, a terminal nucleoside linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group, a locked nucleoside, an abasic nucleoside, a 2'-deoxy-2'-fluoro modified nucleoside, a 2'-amino-modified nucleoside, 2'-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof. Alternatively, an RNA molecule can comprise at least two modified ribonucleosides, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more, up to the entire length of the dsRNA molecule. The modifications need not be the same for each of such a plurality of modified ribonucleosides in an RNA molecule. In one embodiment, modified RNAs contemplated for use in methods and compositions described herein are peptide nucleic acids (PNAs) that have the ability

to form the required duplex structure and that permit or mediate the specific degradation of a target RNA via a RISC pathway.

In one aspect, a modified ribonucleoside includes a deoxy-ribonucleoside. In such an instance, an iRNA agent can comprise one or more deoxynucleosides, including, for example, a deoxynucleoside overhang(s), or one or more deoxynucleosides within the double stranded portion of a dsRNA. However, it is self evident that under no circumstances is a double stranded DNA molecule encompassed by the term "iRNA."

In one aspect, an RNA interference agent includes a single stranded RNA that interacts with a target RNA sequence to direct the cleavage of the target RNA. Without wishing to be bound by theory, long double stranded RNA introduced into plants and invertebrate cells is broken down into siRNA by a Type III endonuclease known as Dicer (Sharp et al., *Genes Dev.* 2001, 15:485). Dicer, a ribonuclease-III-like enzyme, processes the dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, et al., (2001) *Nature* 409:363). The siRNAs are then incorporated into an RNA-induced silencing complex (RISC) where one or more helicases unwind the siRNA duplex, enabling the complementary antisense strand to guide target recognition (Nykanen, et al., (2001) *Cell* 107:309). Upon binding to the appropriate target mRNA, one or more endonucleases within the RISC cleaves the target to induce silencing (Elbashir, et al., (2001) *Genes Dev.* 15:188). Thus, in one aspect the invention relates to a single stranded RNA that promotes the formation of a RISC complex to effect silencing of the target gene.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an iRNA, e.g., a dsRNA. For example, when a 3'-end of one strand of a dsRNA extends beyond the 5'-end of the other strand, or vice versa, there is a nucleotide overhang. A dsRNA can comprise an overhang of at least one nucleotide; alternatively the overhang can comprise at least two nucleotides, at least three nucleotides, at least four nucleotides, at least five nucleotides or more. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) may be on the sense strand, the antisense strand or any combination thereof. Furthermore, the nucleotide(s) of an overhang can be present on the 5' end, 3' end or both ends of either an antisense or sense strand of a dsRNA.

In one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide overhang at the 3' end and/or the 5' end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

The terms "blunt" or "blunt ended" as used herein in reference to a dsRNA mean that there are no unpaired nucleotides or nucleotide analogs at a given terminal end of a dsRNA, i.e., no nucleotide overhang. One or both ends of a dsRNA can be blunt. Where both ends of a dsRNA are blunt, the dsRNA is said to be blunt ended. To be clear, a "blunt ended" dsRNA is a dsRNA that is blunt at both ends, i.e., no nucleotide overhang at either end of the molecule. Most often such a molecule will be double-stranded over its entire length.

The term "antisense strand" or "guide strand" refers to the strand of an iRNA, e.g., a dsRNA, which includes a region that is substantially complementary to a target sequence. As used herein, the term "region of complementarity" refers to the region on the antisense strand that is substantially complementary to a sequence, for example a target sequence, as

defined herein. Where the region of complementarity is not fully complementary to the target sequence, the mismatches may be in the internal or terminal regions of the molecule. Generally, the most tolerated mismatches are in the terminal regions, e.g., within 5, 4, 3, or 2 nucleotides of the 5' and/or 3' terminus.

The term "sense strand," or "passenger strand" as used herein, refers to the strand of an iRNA that includes a region that is substantially complementary to a region of the anti-sense strand as that term is defined herein.

As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle. A SNALP represents a vesicle of lipids coating a reduced aqueous interior comprising a nucleic acid such as an iRNA or a plasmid from which an iRNA is transcribed. SNALPs are described, e.g., in U.S. Patent Application Publication Nos. 20060240093, 20070135372, and in International Application No. WO 2009082817. These applications are incorporated herein by reference in their entirety.

"Introducing into a cell," when referring to an iRNA, means facilitating or effecting uptake or absorption into the cell, as is understood by those skilled in the art. Absorption or uptake of an iRNA can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. The meaning of this term is not limited to cells in vitro; an iRNA may also be "introduced into a cell," wherein the cell is part of a living organism. In such an instance, introduction into the cell will include the delivery to the organism. For example, for in vivo delivery, iRNA can be injected into a tissue site or administered systemically. In vivo delivery can also be by a  $\beta$ -glucan delivery system, such as those described in U.S. Pat. Nos. 5,032,401 and 5,607,677, and U.S. Publication No. 2005/0281781, which are hereby incorporated by reference in their entirety. In vitro introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or known in the art.

As used herein, the term "modulate the expression of," refers to at least partial "inhibition" or partial "activation" of a BCL11A or a KLF1 gene expression in a cell treated with an iRNA composition as described herein compared to the expression of BCL11A or KLF1 in an untreated cell.

The terms "activate," "enhance," "up-regulate the expression of," "increase the expression of," and the like, in so far as they refer to a BCL11A or a KLF1 gene, herein refer to the at least partial activation of the expression of a BCL11A or a KLF1 gene, as manifested by an increase in the amount of BCL11A or KLF1 mRNA, which may be isolated from or detected in a first cell or group of cells in which a BCL11A or a KLF1 gene is transcribed and which has or have been treated such that the expression of a BCL11A or a KLF1 gene is increased, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells).

In one embodiment, expression of a BCL11A or a KLF1 gene is activated by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA as described herein. In some embodiments, a BCL11A or a KLF1 gene is activated by at least about 60%, 70%, or 80% by administration of an iRNA featured in the invention. In some embodiments, expression of a BCL11A or a KLF1 gene is activated by at least about 85%, 90%, or 95% or more by administration of an iRNA as described herein. In some embodiments, the BCL11A or KLF1 gene expression is increased by at least 1-fold, at least 2-fold, at least 5-fold, at least 10-fold, at least 50-fold, at least 100-fold, at least 500-fold, at least 1000 fold or more in cells treated with an iRNA as described herein compared to the expression in an

untreated cell. Activation of expression by small dsRNAs is described, for example, in Li et al., 2006 *Proc. Natl. Acad. Sci. U.S.A.* 103:17337-42, and in US20070111963 and US2005226848, each of which is incorporated herein by reference.

The terms "silence," "inhibit the expression of," "down-regulate the expression of," "suppress the expression of," and the like, in so far as they refer to a BCL11A or a KLF1 gene, herein refer to the at least partial suppression of the expression of a BCL11A or a KLF1 gene, as manifested by a reduction of the amount of BCL11A or KLF1 mRNA which may be isolated from or detected in a first cell or group of cells in which a BCL11A or a KLF1 gene is transcribed and which has or have been treated such that the expression of a BCL11A or a KLF1 gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has or have not been so treated (control cells). The degree of inhibition is usually expressed in terms of

$$\frac{(\text{mRNA in control cells}) - (\text{mRNA in treated cells})}{(\text{mRNA in control cells})} \cdot 100\%$$

Alternatively, the degree of inhibition may be given in terms of a reduction of a parameter that is functionally linked to BCL11A or KLF1 gene expression, e.g., the amount of protein encoded by a BCL11A or a KLF1 gene, or the number of cells displaying a certain phenotype, e.g., lack of or decreased cytokine production. In principle, BCL11A or KLF1 gene silencing may be determined in any cell expressing BCL11A or KLF1, either constitutively or by genomic engineering, and by any appropriate assay. However, when a reference is needed in order to determine whether a given iRNA inhibits the expression of the BCL11A or KLF1 gene by a certain degree and therefore is encompassed by the instant invention, the assays provided in the Examples below shall serve as such reference.

For example, in certain instances, expression of a BCL11A or a KLF1 gene is suppressed by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by administration of an iRNA featured in the invention. In some embodiments, a BCL11A or a KLF1 gene is suppressed by at least about 60%, 70%, or 80% by administration of an iRNA featured in the invention. In some embodiments, a BCL11A or a KLF1 gene is suppressed by at least about 85%, 90%, 95%, 98%, 99%, or more by administration of an iRNA as described herein.

As used herein in the context of BCL11A or KLF1 expression, the terms "treat," "treatment," and the like, refer to relief from or alleviation of pathological processes mediated by BCL11A or KLF1 expression. In the context of the present invention insofar as it relates to any of the other conditions recited herein below (other than pathological processes mediated by BCL11A or KLF1 expression), the terms "treat," "treatment," and the like mean to relieve or alleviate at least one symptom associated with such condition, or to slow or reverse the progression or anticipated progression of such condition, such as slowing the progression of a malignancy or cancer, or increasing the clearance of an infectious organism to alleviate/reduce the symptoms caused by the infection, e.g., hepatitis caused by infection with a hepatitis virus.

By "lower" in the context of a disease marker or symptom is meant a statistically significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at

least 30%, at least 40% or more, and is typically down to a level accepted as within the range of normal for an individual without such disorder.

As used herein, the phrases “therapeutically effective amount” and “prophylactically effective amount” refer to an amount that provides a therapeutic benefit in the treatment, prevention, or management of pathological processes mediated by BCL11A or KLF1 expression or an overt symptom of pathological processes mediated by BCL11A or KLF1 expression. The specific amount that is therapeutically effective can be readily determined by an ordinary medical practitioner, and may vary depending on factors known in the art, such as, for example, the type of pathological processes mediated by BCL11A or KLF1 expression, the patient’s history and age, the stage of pathological processes mediated by BCL11A or KLF1 expression, and the administration of other agents that inhibit pathological processes mediated by BCL11A or KLF1 expression.

As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of an iRNA and a pharmaceutically acceptable carrier. As used herein, “pharmacologically effective amount,” “therapeutically effective amount” or simply “effective amount” refers to that amount of an iRNA effective to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 10% reduction in a measurable parameter associated with a disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 10% reduction in that parameter. For example, a therapeutically effective amount of an iRNA targeting BCL11A or KLF1 can reduce BCL11A or KLF1 protein levels by at least 10%.

The term “pharmaceutically acceptable carrier” refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Agents included in drug formulations are described further herein below.

## II. Double-Stranded Ribonucleic Acid (dsRNA)

Described herein are iRNA agents that inhibit the expression of the BCL11A or KLF1 gene. In one embodiment, the iRNA agent includes double-stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a BCL11A or a KLF1 gene in a cell or mammal, e.g., in a human having a cancer or infectious disease, where the dsRNA includes an antisense strand having a region of complementarity which is complementary to at least a part of an mRNA formed in the expression of a BCL11A or a KLF1 gene, and where the region of complementarity is 30 nucleotides or less in length, generally 19-24 nucleotides in length, and where the dsRNA, upon contact with a cell expressing the BCL11A or a KLF1 gene, inhibits the expression of the BCL11A or KLF1 gene by at least 10% as assayed by, for

example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by Western blot. In one embodiment, the iRNA agent activates the expression of a BCL11A or a KLF1 gene in a cell or mammal. Expression of a BCL11A or a KLF1 gene in cell culture, such as in COS cells, HeLa cells, primary hepatocytes, HepG2 cells, primary cultured cells or in a biological sample from a subject can be assayed by measuring BCL11A or KLF1 mRNA levels, such as by bDNA or TaqMan assay, or by measuring protein levels, such as by immunofluorescence analysis, using, for example, Western Blotting or flow cytometric techniques.

A dsRNA includes two RNA strands that are sufficiently complementary to hybridize to form a duplex structure under conditions in which the dsRNA will be used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, and generally fully complementary, to a target sequence, derived from the sequence of an mRNA formed during the expression of a BCL11A or a KLF1 gene. The other strand (the sense strand) includes a region that is complementary to the antisense strand, such that the two strands hybridize and form a duplex structure when combined under suitable conditions. Generally, the duplex structure is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 base pairs in length, inclusive. Similarly, the region of complementarity to the target sequence is between 15 and 30 inclusive, more generally between 18 and 25 inclusive, yet more generally between 19 and 24 inclusive, and most generally between 19 and 21 nucleotides in length, inclusive. In some embodiments, the dsRNA is between 15 and 20 nucleotides in length, inclusive, and in other embodiments, the dsRNA is between 25 and 30 nucleotides in length, inclusive. As the ordinarily skilled person will recognize, the targeted region of an RNA targeted for cleavage will most often be part of a larger RNA molecule, often an mRNA molecule. Where relevant, a “part” of an mRNA target is a contiguous sequence of an mRNA target of sufficient length to be a substrate for RNAi-directed cleavage (i.e., cleavage through a RISC pathway). dsRNAs having duplexes as short as 9 base pairs can, under some circumstances, mediate RNAi-directed RNA cleavage. Most often a target will be at least 15 nucleotides in length, e.g., 15-30 nucleotides in length.

One of skill in the art will also recognize that the duplex region is a primary functional portion of a dsRNA, e.g., a duplex region of 9 to 36, e.g., 15-30 base pairs. Thus, in one embodiment, to the extent that it becomes processed to a functional duplex of e.g., 15-30 base pairs that targets a desired RNA for cleavage, an RNA molecule or complex of RNA molecules having a duplex region greater than 30 base pairs is a dsRNA. Thus, an ordinarily skilled artisan will recognize that in one embodiment, then, an miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an iRNA agent useful to target BCL11A or KLF1 expression is not generated in the target cell by cleavage of a larger dsRNA.

A dsRNA as described herein may further include one or more single-stranded nucleotide overhangs. The dsRNA can be synthesized by standard methods known in the art as further discussed below, e.g., by use of an automated DNA synthesizer, such as are commercially available from, for example, Biosearch, Applied Biosystems, Inc. In one embodiment, a BCL11A or a KLF1 gene is a human BCL11A or a KLF1 gene. In another embodiment the BCL11A or a KLF1 gene is a mouse or a rat BCL11A or KLF1 gene. In specific embodiments, the first sequence is a sense strand of a dsRNA that includes a sense sequence from Table 2A-1,

2A-2, 2A-3, Table 2B, or Table 2C, or Tables 3-7, and the second sequence is an antisense strand of a dsRNA that includes an antisense sequence from Table 2A-1, 2A-2, 2A-3, Table 2B, or Table 2C, or Tables 3-7. Alternative dsRNA agents that target sequences other than those of the dsRNAs of Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3-7 can readily be determined using the target sequence and the flanking BCL11A or KLF1 sequence.

In one aspect, a dsRNA will include at least nucleotide sequences, whereby the sense strand is selected from the groups of sequences provided in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and in Table 3-7, and the corresponding antisense strand of the sense strand selected from Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3-7. In this aspect, one of the two sequences is complementary to the other of the two sequences, with one of the sequences being substantially complementary to a sequence of an mRNA generated by the expression of a BCL11A or KLF1 gene. As such, in this aspect, a dsRNA will include two oligonucleotides, where one oligonucleotide is described as the sense strand in Table 2A-1, 2A-2, 2A-3, Table 2B, or Table 2C, or Tables 3-7, and the second oligonucleotide is described as the corresponding antisense strand of the sense strand from Table 2A-1, 2A-2, 2A-3, Table 2B, or Table 2C, or Tables 3-7. As described elsewhere herein and as known in the art, the complementary sequences of a dsRNA can also be contained as self-complementary regions of a single nucleic acid molecule, as opposed to being on separate oligonucleotides.

The skilled person is well aware that dsRNAs having a duplex structure of between 20 and 23, but specifically 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir et al., EMBO 2001, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can be effective as well. In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7, dsRNAs described herein can include at least one strand of a length of minimally 21 nt. It can be reasonably expected that shorter duplexes having one of the sequences of Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7 minus only a few nucleotides on one or both ends may be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a partial sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides from one of the sequences of Table 2A-1, 2A-2, 2A-3, Table 2B, or Table 2C, or Tables 3-7, and differing in their ability to inhibit the expression of a BCL11A or a KLF1 gene by not more than 5, 10, 15, 20, 25, or 30% inhibition from a dsRNA comprising the full sequence, are contemplated according to the invention.

In addition, the RNAs provided in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7, identify a site in a BCL11A or a KLF1 transcript that is susceptible to RISC-mediated cleavage. As such, the present invention further features iRNAs that target within one of such sequences. As used herein, an iRNA is said to target within a particular site of an RNA transcript if the iRNA promotes cleavage of the transcript anywhere within that particular site. Such an iRNA will generally include at least 15 contiguous nucleotides from one of the sequences provided in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7 coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a BCL11A or a KLF1 gene.

While a target sequence is generally 15-30 nucleotides in length, there is wide variation in the suitability of particular

sequences in this range for directing cleavage of any given target RNA. Various software packages and the guidelines set out herein provide guidance for the identification of optimal target sequences for any given gene target, but an empirical approach can also be taken in which a "window" or "mask" of a given size (as a non-limiting example, 21 nucleotides) is literally or figuratively (including, e.g., in silico) placed on the target RNA sequence to identify sequences in the size range that may serve as target sequences. By moving the sequence "window" progressively one nucleotide upstream or downstream of an initial target sequence location, the next potential target sequence can be identified, until the complete set of possible sequences is identified for any given target size selected. This process, coupled with systematic synthesis and testing of the identified sequences (using assays as described herein or as known in the art) to identify those sequences that perform optimally can identify those RNA sequences that, when targeted with an iRNA agent, mediate the best inhibition of target gene expression. Thus, while the sequences identified, for example, in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7 represent effective target sequences, it is contemplated that further optimization of inhibition efficiency can be achieved by progressively "walking the window" one nucleotide upstream or downstream of the given sequences to identify sequences with equal or better inhibition characteristics.

Further, it is contemplated that for any sequence identified, e.g., in Table 2A-1, 2A-2, 2A-3, Table 2B, and Table 2C, and Tables 3, 4, 5, 6 and 7, further optimization could be achieved by systematically either adding or removing nucleotides to generate longer or shorter sequences and testing those and sequences generated by walking a window of the longer or shorter size up or down the target RNA from that point. Again, coupling this approach to generating new candidate targets with testing for effectiveness of iRNAs based on those target sequences in an inhibition assay as known in the art or as described herein can lead to further improvements in the efficiency of inhibition. Further still, such optimized sequences can be adjusted by, e.g., the introduction of modified nucleotides as described herein or as known in the art, addition or changes in overhang, or other modifications as known in the art and/or discussed herein to further optimize the molecule (e.g., increasing serum stability or circulating half-life, increasing thermal stability, enhancing transmembrane delivery, targeting to a particular location or cell type, increasing interaction with silencing pathway enzymes, increasing release from endosomes, etc.) as an expression inhibitor.

An iRNA as described herein can contain one or more mismatches to the target sequence. In one embodiment, an iRNA as described herein contains no more than 3 mismatches. If the antisense strand of the iRNA contains mismatches to a target sequence, it is preferable that the area of mismatch not be located in the center of the region of complementarity. If the antisense strand of the iRNA contains mismatches to the target sequence, it is preferable that the mismatch be restricted to be within the last 5 nucleotides from either the 5' or 3' end of the region of complementarity. For example, for a 23 nucleotide iRNA agent RNA strand which is complementary to a region of a BCL11A or a KLF1 gene, the RNA strand generally does not contain any mismatch within the central 13 nucleotides. The methods described herein or methods known in the art can be used to determine whether an iRNA containing a mismatch to a target sequence is effective in inhibiting the expression of a BCL11A or a KLF1 gene. Consideration of the efficacy of iRNAs with mismatches in inhibiting expression of a BCL11A or a KLF1

gene is important, especially if the particular region of complementarity in a BCL11A or a KLF1 gene is known to have polymorphic sequence variation within the population.

In one embodiment, at least one end of a dsRNA has a single-stranded nucleotide overhang of 1 to 4, generally 1 or 2 nucleotides. dsRNAs having at least one nucleotide overhang have unexpectedly superior inhibitory properties relative to their blunt-ended counterparts. In yet another embodiment, the RNA of an iRNA, e.g., a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. The nucleic acids featured in the invention may be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference. Modifications include, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, conjugation, inverted linkages, etc.) 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, removal of bases (abasic nucleotides), or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNA compounds useful in this invention include, but are not limited to RNAs containing modified backbones or no natural internucleoside linkages. RNAs having modified backbones include, among others, those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified RNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In particular embodiments, the modified RNA will have a phosphorus atom in its internucleoside backbone.

Modified RNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat. RE39464, each of which is herein incorporated by reference.

Modified RNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleo-

side linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH<sub>2</sub> component parts.

Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

In other RNA mimetics suitable or contemplated for use in iRNAs, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an RNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of an RNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen et al., Science, 1991, 254, 1497-1500.

Some embodiments featured in the invention include RNAs with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular —CH<sub>2</sub>—NH—CH<sub>2</sub>—, —CH<sub>2</sub>—N(CH<sub>3</sub>)—O—CH<sub>2</sub>— [known as a methylene (methylimino) or MMI backbone], —CH<sub>2</sub>—O—N(CH<sub>3</sub>)—CH<sub>2</sub>—, —CH<sub>2</sub>—N(CH<sub>3</sub>)—N(CH<sub>3</sub>)—CH<sub>2</sub>— and —N(CH<sub>3</sub>)—CH<sub>2</sub>—CH<sub>2</sub>— [wherein the native phosphodiester backbone is represented as —O—P—O—CH<sub>2</sub>—] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

Modified RNAs may also contain one or more substituted sugar moieties. The iRNAs, e.g., dsRNAs, featured herein can include one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C<sub>1</sub> to C<sub>10</sub> alkyl or C<sub>2</sub> to C<sub>10</sub> alkenyl and alkynyl. Exemplary suitable modifications include O[(CH<sub>2</sub>)<sub>n</sub>O]<sub>m</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>OCH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>NH<sub>2</sub>, O(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>, O(CH<sub>2</sub>)<sub>n</sub>ONH<sub>2</sub>, and O(CH<sub>2</sub>)<sub>n</sub>ON[(CH<sub>2</sub>)<sub>n</sub>CH<sub>3</sub>]<sub>2</sub>, where n and m are from 1 to about 10. In other embodiments, dsRNAs include one of the following at the 2' position: C<sub>1</sub> to C<sub>10</sub> lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH<sub>3</sub>, OCN, Cl, Br, CN, CF<sub>3</sub>, OCF<sub>3</sub>, SOCH<sub>3</sub>, SO<sub>2</sub>CH<sub>3</sub>, ONO<sub>2</sub>, NO<sub>2</sub>, N<sub>3</sub>, NH<sub>2</sub>, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an iRNA, or a group for improving the pharmacodynamic properties of an iRNA, and

other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O—CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78:486-504) i.e., an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminoethoxy, i.e., a O(CH<sub>2</sub>)<sub>2</sub>ON (CH<sub>3</sub>)<sub>2</sub> group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O—CH<sub>2</sub>—O—CH<sub>2</sub>—N(CH<sub>3</sub>)<sub>2</sub>, also described in examples herein below.

Other modifications include 2'-methoxy (2'-OCH<sub>3</sub>), 2'-aminopropoxy (2'-OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the RNA of an iRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. iRNAs may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference.

An iRNA may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J. L., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie, International Edition*, 1991, 30, 613, and those disclosed by Sanghvi, Y. S., Chapter 15, *dsRNA Research and Applications*, pages 289-302, Croke, S. T. and Lebleu, B., Ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. (Sanghvi, Y. S., Croke, S. T. and Lebleu, B., Eds., *dsRNA Research and Applications*, CRC Press, Boca Raton,

1993, pp. 276-278) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121; 5,596,091; 5,614,617; 5,681,941; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, each of which is herein incorporated by reference, and U.S. Pat. No. 5,750,692, also herein incorporated by reference.

The RNA of an iRNA can also be modified to include one or more locked nucleic acids (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. This structure effectively "locks" the ribose in the 3'-endo structural conformation. The addition of locked nucleic acids to siRNAs has been shown to increase siRNA stability in serum, and to reduce off-target effects (Elmen, J. et al., (2005) *Nucleic Acids Research* 33(1):439-447; Mook, O R. et al., (2007) *Mol Canc Ther* 6(3):833-843; Grunweller, A. et al., (2003) *Nucleic Acids Research* 31(12):3185-3193).

Representative U.S. patents that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; and 7,399,845, each of which is herein incorporated by reference in its entirety.

Another modification of the RNA of an iRNA featured in the invention involves chemically linking to the RNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6553-6556), cholic acid (Manoharan et al., *Biorg. Med. Chem. Lett.*, 1994, 4:1053-1060), a thioether, e.g., beryl-5-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660:306-309; Manoharan et al., *Biorg. Med. Chem. Lett.*, 1993, 3:2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20:533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., *EMBO J*, 1991, 10:1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259:327-330; Svinarchuk et al., *Biochimie*, 1993, 75:49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36:3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., *Nucleosides & Nucleotides*, 1995, 14:969-973), or adamantane acetic acid (Manoharan et al., *Tetrahedron Lett.*, 1995, 36:3651-3654), a palmitoyl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264:229-237), or an octadecylamine or hexylamino-carboxycholesterol moiety (Croke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277:923-937).

In one embodiment, a ligand alters the distribution, targeting or lifetime of an iRNA agent into which it is incorporated. In some embodiments, a ligand provides an enhanced affinity for a selected target, e.g. molecule, cell or cell type, compartment, e.g., a cellular or organ compartment, tissue, organ or region of the body, as, e.g., compared to a species absent such as a ligand. Typical ligands will not take part in duplex pairing in a duplexed nucleic acid.

Ligands can include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid. Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolide) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacrylic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an  $\alpha$  helical peptide.

Ligands can also include targeting groups, e.g., a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B 12, biotin, or an RGD peptide or RGD peptide mimetic.

Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g. cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O (hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, phosphate, amino, mercapto, PEG (e.g., PEG-40K), MPEG, [MPEG]<sub>2</sub>, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid), synthetic ribonucleases (e.g., imidazole, bisimidazole, histamine, imidazole clusters, acridine-imidazole conjugates, Eu3+ complexes of tetraazamacrocycles), dinitrophenyl, HRP, or AP.

Ligands can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Ligands may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose. The ligand can be, for example, a lipopolysaccharide, an activator of p38 MAP kinase, or an activator of NF- $\kappa$ B.

The ligand can be a substance, e.g., a drug, which can increase the uptake of the iRNA agent into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or inter-

mediate filaments. The drug can be, for example, taxon, vincristine, vinblastine, cytochalasin, nocodazole, japlakinolide, latrunculin A, phalloidin, swinholide A, indanocine, or myoservin.

In one ligand, the ligand is a lipid or lipid-based molecule. Such a lipid or lipid-based molecule can typically bind a serum protein, such as human serum albumin (HSA). An HSA binding ligand allows for distribution of the conjugate to a target tissue, e.g., a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, neproxin or aspirin can be used. A lipid or lipid-based ligand can (a) increase resistance to degradation of the conjugate, (b) increase targeting or transport into a target cell or cell membrane, and/or (c) can be used to adjust binding to a serum protein, e.g., HSA.

A lipid based ligand can be used to modulate, e.g., control the binding of the conjugate to a target tissue. For example, a lipid or lipid-based ligand that binds to HSA more strongly will be less likely to be targeted to the kidney and therefore less likely to be cleared from the body. A lipid or lipid-based ligand that binds to HSA less strongly can be used to target the conjugate to the kidney.

In one embodiment, the lipid based ligand binds HSA. For example, the ligand can bind HSA with a sufficient affinity such that distribution of the conjugate to a non-kidney tissue is enhanced. However, the affinity is typically not so strong that the HSA-ligand binding cannot be reversed.

In another embodiment, the lipid based ligand binds HSA weakly or not at all, such that distribution of the conjugate to the kidney is enhanced. Other moieties that target to kidney cells can also be used in place of or in addition to the lipid based ligand.

In another aspect, the ligand is a moiety, e.g., a vitamin, which is taken up by a target cell, e.g., a proliferating cell. These are particularly useful for treating disorders characterized by unwanted cell proliferation, e.g., of the malignant or non-malignant type, e.g., cancer cells. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include are B vitamin, e.g., folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up by cancer cells. Also included are HSA and low density lipoprotein (LDL).

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In one embodiment, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopodia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is typically an  $\alpha$ -helical agent, and can have a lipophilic and a lipophobic phase.

The ligand can be a peptide or peptidomimetic. A peptidomimetic (also referred to herein as an oligopeptidomimetic) is a molecule capable of folding into a defined three-dimensional structure similar to a natural peptide. The attachment of peptide and peptidomimetics to iRNA agents can affect pharmacokinetic distribution of the iRNA, such as by enhancing cellular recognition and absorption. The peptide or peptidomimetic moiety can be about 5-50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

A peptide or peptidomimetic can be, for example, a cell permeation peptide, cationic peptide, amphipathic peptide, or hydrophobic peptide (e.g., consisting primarily of Tyr, Trp or Phe). The peptide moiety can be a dendrimer peptide, constrained peptide or crosslinked peptide. In another alternative, the peptide moiety can include a hydrophobic membrane translocation sequence (MTS). An exemplary hydrophobic

MTS-containing peptide is RFGF having the amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:1). An RFGF analogue (e.g., amino acid sequence AALLPVLLAAP (SEQ ID NO:2)) containing a hydrophobic MTS can also be a targeting moiety. The peptide moiety can be a "delivery" peptide, which can carry large polar molecules including peptides, oligonucleotides, and protein across cell membranes. For example, sequences from the HIV Tat protein (GRKKRRQRRRPPQ (SEQ ID NO:3)) and the *Drosophila Antennapedia* protein (RQIKIWQNRRMKWKK (SEQ ID NO: 4)) have been found to be capable of functioning as delivery peptides. A peptide or peptidomimetic can be encoded by a random sequence of DNA, such as a peptide identified from a phage-display library, or one-bead-one-compound (OBOC) combinatorial library (Lam et al., Nature, 354:82-84, 1991). Typically, the peptide or peptidomimetic tethered to a dsRNA agent via an incorporated monomer unit is a cell targeting peptide such as an arginine-glycine-aspartic acid (RGD)-peptide, or RGD mimic. A peptide moiety can range in length from about 5 amino acids to about 40 amino acids. The peptide moieties can have a structural modification, such as to increase stability or direct conformational properties. Any of the structural modifications described below can be utilized.

An RGD peptide moiety can be used to target a tumor cell, such as an endothelial tumor cell or a breast cancer tumor cell (Zitzmann et al., Cancer Res., 62:5139-43, 2002). An RGD peptide can facilitate targeting of an dsRNA agent to tumors of a variety of other tissues, including the lung, kidney, spleen, or liver (Aoki et al., Cancer Gene Therapy 8:783-787, 2001). Typically, the RGD peptide will facilitate targeting of an iRNA agent to the kidney. The RGD peptide can be linear or cyclic, and can be modified, e.g., glycosylated or methylated to facilitate targeting to specific tissues. For example, a glycosylated RGD peptide can deliver a iRNA agent to a tumor cell expressing  $\alpha_v\beta_3$  (Haubner et al., Jour. Nucl. Med., 42:326-336, 2001).

A "cell permeation peptide" is capable of permeating a cell, e.g., a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an  $\alpha$ -helical linear peptide (e.g., LL-37 or Ceropin P1), a disulfide bond-containing peptide (e.g.,  $\alpha$ -defensin,  $\beta$ -defensin or bactenecin), or a peptide containing only one or two dominating amino acids (e.g., PR-39 or indolicidin). A cell permeation peptide can also include a nuclear localization signal (NLS). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni et al., Nucl. Acids Res. 31:2717-2724, 2003).

Representative U.S. patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241; 5,391,723; 5,416,203; 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; each of which is herein incorporated by reference.

It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are chimeric compounds. "Chimeric" iRNA compounds, or "chimeras," in the context of the present invention, are iRNA compounds, e.g., dsRNAs, that contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of a dsRNA compound. These iRNAs typically contain at least one region wherein the RNA is modified so as to confer upon the iRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the iRNA may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of iRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter iRNAs when chimeric dsRNAs are used, compared to phosphorothioate deoxy dsRNAs hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

In certain instances, the RNA of an iRNA can be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to iRNAs in order to enhance the activity, cellular distribution or cellular uptake of the iRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Kubo, T. et al., Biochem. Biophys. Res. Comm., 2007, 365(1):54-61; Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86:6553), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4:1053), a thioether, e.g., hexyl-5-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306; Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3:2765), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10:111; Kabanov et al., FEBS Lett., 1990, 259:327; Svinarchuk et al., Biochimie, 1993, 75:49), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651; Shea et al., Nucl. Acids Res., 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923). Representative United States patents that teach the preparation of such RNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of an RNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the RNA still bound to the solid support or following cleavage of the RNA, in solution phase. Purification of the RNA conjugate by HPLC typically affords the pure conjugate.

### Delivery of iRNA

The delivery of an iRNA to a subject in need thereof can be achieved in a number of different ways. In vivo delivery can be performed directly by administering a composition comprising an iRNA, e.g. a dsRNA, to a subject. Alternatively, delivery can be performed indirectly by administering one or more vectors that encode and direct the expression of the iRNA. These alternatives are discussed further below.

### Direct Delivery

In general, any method of delivering a nucleic acid molecule can be adapted for use with an iRNA (see e.g., Akhtar S. and Julian R L. (1992) *Trends Cell. Biol.* 2(5):139-144 and WO94/02595, which are incorporated herein by reference in their entireties). However, there are three factors that are important to consider in order to successfully deliver an iRNA molecule in vivo: (a) biological stability of the delivered molecule, (2) preventing non-specific effects, and (3) accumulation of the delivered molecule in the target tissue. The non-specific effects of an iRNA can be minimized by local administration, for example by direct injection or implantation into a tissue (as a non-limiting example, a tumor) or topically administering the preparation. Local administration to a treatment site maximizes local concentration of the agent, limits the exposure of the agent to systemic tissues that may otherwise be harmed by the agent or that may degrade the agent, and permits a lower total dose of the iRNA molecule to be administered. Several studies have shown successful knockdown of gene products when an iRNA is administered locally. For example, intraocular delivery of a VEGF dsRNA by intravitreal injection in cynomolgus monkeys (Tolentino, M J., et al (2004) *Retina* 24:132-138) and subretinal injections in mice (Reich, S J., et al (2003) *Mol. Vis.* 9:210-216) were both shown to prevent neovascularization in an experimental model of age-related macular degeneration. In addition, direct intratumoral injection of a dsRNA in mice reduces tumor volume (Pille, J., et al (2005) *Mol. Ther.* 11:267-274) and can prolong survival of tumor-bearing mice (Kim, W J., et al (2006) *Mol. Ther.* 14:343-350; Li, S., et al (2007) *Mol. Ther.* 15:515-523). RNA interference has also shown success with local delivery to the CNS by direct injection (Dorn, G., et al. (2004) *Nucleic Acids* 32:e49; Tan, P H., et al (2005) *Gene Ther.* 12:59-66; Makimura, H., et al (2002) *BMC Neurosci.* 3:18; Shishkina, G T., et al (2004) *Neuroscience* 129: 521-528; Thakker, E R., et al (2004) *Proc. Natl. Acad. Sci. U.S.A.* 101:17270-17275; Akaneya, Y., et al (2005) *J. Neurophysiol.* 93:594-602) and to the lungs by intranasal administration (Howard, K A., et al (2006) *Mol. Ther.* 14:476-484; Zhang, X., et al (2004) *J. Biol. Chem.* 279:10677-10684; Bitko, V., et al (2005) *Nat. Med.* 11:50-55). For administering an iRNA systemically for the treatment of a disease, the RNA can be modified or alternatively delivered using a drug delivery system; both methods act to prevent the rapid degradation of the dsRNA by endo- and exo-nucleases in vivo. Modification of the RNA or the pharmaceutical carrier can also permit targeting of the iRNA composition to the target tissue and avoid undesirable off-target effects. iRNA molecules can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an iRNA directed against ApoB conjugated to a lipophilic cholesterol moiety was injected systemically into mice and resulted in knockdown of apoB mRNA in both the liver and jejunum (Soutschek, J., et al (2004) *Nature* 432:173-178). Conjugation of an iRNA to an aptamer has been shown to inhibit tumor growth and mediate tumor regression in a mouse model of prostate cancer (McNamara, J O., et al (2006) *Nat. Biotechnol.* 24:1005-1015). In an alternative embodiment, the iRNA can be delivered using

drug delivery systems such as a nanoparticle, a dendrimer, a polymer, liposomes, or a cationic delivery system. Positively charged cationic delivery systems facilitate binding of an iRNA molecule (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an iRNA by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an iRNA, or induced to form a vesicle or micelle (see e.g., Kim S H., et al (2008) *Journal of Controlled Release* 129(2):107-116) that encases an iRNA. The formation of vesicles or micelles further prevents degradation of the iRNA when administered systemically. Methods for making and administering cationic-iRNA complexes are well within the abilities of one skilled in the art (see e.g., Sorensen, D R., et al (2003) *J. Mol. Biol.* 327:761-766; Verma, U N., et al (2003) *Clin. Cancer Res.* 9:1291-1300; Arnold, A S et al (2007) *J. Hypertens.* 25:197-205, which are incorporated herein by reference in their entirety). Some non-limiting examples of drug delivery systems useful for systemic delivery of iRNAs include DOTAP (Sorensen, D R., et al (2003), supra; Verma, U N., et al (2003), supra), Oligofectamine, "solid nucleic acid lipid particles" (Zimmermann, T S., et al (2006) *Nature* 441:111-114), cardiolipin (Chien, P Y., et al (2005) *Cancer Gene Ther.* 12:321-328; Pal, A., et al (2005) *Int J. Oncol.* 26:1087-1091), polyethyleneimine (Bonnet M E., et al (2008) *Pharm. Res.* August 16 Epub ahead of print; Aigner, A. (2006) *J. Biomed. Biotechnol.* 71659), Arg-Gly-Asp (RGD) peptides (Liu, S. (2006) *Mol. Pharm.* 3:472-487), and polyamidoamines (Tomalia, D A., et al (2007) *Biochem. Soc. Trans.* 35:61-67; Yoo, H., et al (1999) *Pharm. Res.* 16:1799-1804). In some embodiments, an iRNA forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of iRNAs and cyclodextrins can be found in U.S. Pat. No. 7,427,605, which is herein incorporated by reference in its entirety.

### Vector Encoded dsRNAs

In another aspect, iRNA targeting the BCL11A or KLF1 gene can be expressed from transcription units inserted into DNA or RNA vectors (see, e.g., Couture, A, et al., *TIG.* (1996), 12:5-10; Skillern, A., et al., International PCT Publication No. WO 00/22113, Conrad, International PCT Publication No. WO 00/22114, and Conrad, U.S. Pat. No. 6,054, 299). Expression can be transient (on the order of hours to weeks) or sustained (weeks to months or longer), depending upon the specific construct used and the target tissue or cell type. These transgenes can be introduced as a linear construct, a circular plasmid, or a viral vector, which can be an integrating or non-integrating vector. The transgene can also be constructed to permit it to be inherited as an extrachromosomal plasmid (Gassmann, et al., *Proc. Natl. Acad. Sci. USA* (1995) 92:1292).

The individual strand or strands of an iRNA can be transcribed from a promoter on an expression vector. Where two separate strands are to be expressed to generate, for example, a dsRNA, two separate expression vectors can be co-introduced (e.g., by transfection or infection) into a target cell. Alternatively each individual strand of a dsRNA can be transcribed by promoters both of which are located on the same expression plasmid. In one embodiment, a dsRNA is expressed as an inverted repeat joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

An iRNA expression vector is typically a DNA plasmid or viral vector. An expression vector compatible with eukaryotic cells, e.g., with vertebrate cells, can be used to produce recombinant constructs for the expression of an iRNA as described herein. Eukaryotic cell expression vectors are well

known in the art and are available from a number of commercial sources. Typically, such vectors contain convenient restriction sites for insertion of the desired nucleic acid segment. Delivery of iRNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that allows for introduction into a desired target cell.

An iRNA expression plasmid can be transfected into a target cell as a complex with a cationic lipid carrier (e.g., Oligofectamine) or a non-cationic lipid-based carrier (e.g., Transit-TKO™). Multiple lipid transfections for iRNA-mediated knockdowns targeting different regions of a target RNA over a period of a week or more are also contemplated by the invention. Successful introduction of vectors into host cells can be monitored using various known methods. For example, transient transfection can be signaled with a reporter, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Stable transfection of cells ex vivo can be ensured using markers that provide the transfected cell with resistance to specific environmental factors (e.g., antibiotics and drugs), such as hygromycin B resistance.

Viral vector systems which can be utilized with the methods and compositions described herein include, but are not limited to, (a) adenovirus vectors; (b) retrovirus vectors, including but not limited to lentiviral vectors, moloney murine leukemia virus, etc.; (c) adeno-associated virus vectors; (d) herpes simplex virus vectors; (e) SV40 vectors; (f) polyoma virus vectors; (g) papilloma virus vectors; (h) picornavirus vectors; (i) pox virus vectors such as an orthopox, e.g., vaccinia virus vectors or avipox, e.g. canary pox or fowl pox; and (j) a helper-dependent or gutless adenovirus. Replication-defective viruses can also be advantageous. Different vectors will or will not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct may be incorporated into vectors capable of episomal replication, e.g. EPV and EBV vectors. Constructs for the recombinant expression of an iRNA will generally require regulatory elements, e.g., promoters, enhancers, etc., to ensure the expression of the iRNA in target cells. Other aspects to consider for vectors and constructs are further described below.

Vectors useful for the delivery of an iRNA will include regulatory elements (promoter, enhancer, etc.) sufficient for expression of the iRNA in the desired target cell or tissue. The regulatory elements can be chosen to provide either constitutive or regulated/inducible expression.

Expression of the iRNA can be precisely regulated, for example, by using an inducible regulatory sequence that is sensitive to certain physiological regulators, e.g., circulating glucose levels, or hormones (Docherty et al., 1994, FASEB J. 8:20-24). Such inducible expression systems, suitable for the control of dsRNA expression in cells or in mammals include, for example, regulation by ecdysone, by estrogen, progesterone, tetracycline, chemical inducers of dimerization, and isopropyl- $\beta$ -D-1-thiogalactopyranoside (IPTG). A person skilled in the art would be able to choose the appropriate regulatory/promoter sequence based on the intended use of the iRNA transgene.

In a specific embodiment, viral vectors that contain nucleic acid sequences encoding an iRNA can be used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding an iRNA are cloned into one or more vectors, which facilitates delivery of the nucleic acid

into a patient. More detail about retroviral vectors can be found, for example, in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993). Lentiviral vectors contemplated for use include, for example, the HIV based vectors described in U.S. Pat. Nos. 6,143,520; 5,665,557; and 5,981,276, which are herein incorporated by reference.

Adenoviruses are also contemplated for use in delivery of iRNAs. Adenoviruses are especially attractive vehicles, e.g., for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). A suitable AV vector for expressing an iRNA featured in the invention, a method for constructing the recombinant AV vector, and a method for delivering the vector into target cells, are described in Xia H et al. (2002), *Nat. Biotech.* 20: 1006-1010.

Use of Adeno-associated virus (AAV) vectors is also contemplated (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Pat. No. 5,436,146). In one embodiment, the iRNA can be expressed as two separate, complementary single-stranded RNA molecules from a recombinant AAV vector having, for example, either the U6 or H1 RNA promoters, or the cytomegalovirus (CMV) promoter. Suitable AAV vectors for expressing the dsRNA featured in the invention, methods for constructing the recombinant AV vector, and methods for delivering the vectors into target cells are described in Samulski R et al. (1987), *J. Virol.* 61: 3096-3101; Fisher K J et al. (1996), *J. Virol.* 70: 520-532; Samulski R et al. (1989), *J. Virol.* 63: 3822-3826; U.S. Pat. No. 5,252,479; U.S. Pat. No. 5,139,941; International Patent Application No. WO 94/13788; and International Patent Application No. WO 93/24641, the entire disclosures of which are herein incorporated by reference.

Another typical viral vector is a pox virus such as a vaccinia virus, for example an attenuated vaccinia such as Modified Virus Ankara (MVA) or NYVAC, an avipox such as fowl pox or canary pox.

The tropism of viral vectors can be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses, or by substituting different viral capsid proteins, as appropriate. For example, lentiviral vectors can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like. AAV vectors can be made to target different cells by engineering the vectors to express different capsid protein sero-

types; see, e.g., Rabinowitz J E et al. (2002), J Virol 76:791-801, the entire disclosure of which is herein incorporated by reference.

The pharmaceutical preparation of a vector can include the vector in an acceptable diluent, or can include a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

### III. Pharmaceutical Compositions Containing iRNA

In one embodiment, the invention provides pharmaceutical compositions containing an iRNA, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical composition containing the iRNA is useful for treating a disease or disorder associated with the expression or activity of a BCL11A or a KLF1 gene, such as pathological processes mediated by BCL11A or KLF1 expression. Such pharmaceutical compositions are formulated based on the mode of delivery. For example, compositions can be formulated for systemic administration via parenteral delivery, e.g., by intravenous (IV) delivery, or compositions can be formulated for direct delivery into the brain parenchyma, e.g., by infusion into the brain, such as by continuous pump infusion.

The pharmaceutical compositions featured herein are administered in dosages sufficient to inhibit expression of BCL11A or KLF1 genes. In general, a suitable dose of iRNA will be in the range of 0.01 to 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of 1 to 50 mg per kilogram body weight per day. For example, the dsRNA can be administered at 0.05 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg, or 50 mg/kg per single dose. The pharmaceutical composition may be administered once daily, or the iRNA may be administered as two, three, or more sub-doses at appropriate intervals throughout the day or even using continuous infusion or delivery through a controlled release formulation. In that case, the iRNA contained in each sub-dose must be correspondingly smaller in order to achieve the total daily dosage. The dosage unit can also be compounded for delivery over several days, e.g., using a conventional sustained release formulation which provides sustained release of the iRNA over a several day period. Sustained release formulations are well known in the art and are particularly useful for delivery of agents at a particular site, such as could be used with the agents of the present invention. In this embodiment, the dosage unit contains a corresponding multiple of the daily dose.

The effect of a single dose on BCL11A or KLF1 levels can be long lasting, such that subsequent doses are administered at not more than 3, 4, or 5 day intervals, or at not more than 1, 2, 3, or 4 week intervals.

The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a composition can include a single treatment or a series of treatments. Estimates of effective dosages and in vivo half-lives for the individual iRNAs encompassed by the invention can be made using conventional methodologies or on the basis of in vivo testing using an appropriate animal model, as described elsewhere herein.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as pathological processes mediated by BCL11A or KLF1

expression. Such models can be used for in vivo testing of iRNA, as well as for determining a therapeutically effective dose. A suitable mouse model is, for example, a mouse containing a transgene expressing human BCL11A or KLF1.

The present invention also includes pharmaceutical compositions and formulations that include the iRNA compounds featured in the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (e.g., by a transdermal patch), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; subdermal, e.g., via an implanted device; or intracranial, e.g., by intraparenchymal, intrathecal or intraventricular, administration.

The iRNA can be delivered in a manner to target a particular tissue, such as a tissue that produces erythrocytes. For example, the iRNA can be delivered to bone marrow, liver (e.g., hepatocytes of liver), lymph glands, spleen, lungs (e.g., pleura of lungs) or spine. In one embodiment, the iRNA is delivered to bone marrow.

Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful. Suitable topical formulations include those in which the iRNAs featured in the invention are in admixture with a topical delivery agent such as lipids, liposomes, fatty acids, fatty acid esters, steroids, chelating agents and surfactants. Suitable lipids and liposomes include neutral (e.g., dioleoylphosphatidyl DOPE ethanolamine, dimyristoylphosphatidyl choline DMPC, distearylphosphatidyl choline) negative (e.g., dimyristoylphosphatidyl glycerol DMPG) and cationic (e.g., dioleoyltetramethylaminopropyl DOTAP and dioleoylphosphatidyl ethanolamine DOTMA). iRNAs featured in the invention may be encapsulated within liposomes or may form complexes thereto, in particular to cationic liposomes. Alternatively, iRNAs may be complexed to lipids, in particular to cationic lipids. Suitable fatty acids and esters include but are not limited to arachidonic acid, oleic acid, eicosanoic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a C<sub>1-20</sub> alkyl ester (e.g., isopropylmyristate IPM), monoglyceride, diglyceride or pharmaceutically acceptable salt thereof. Topical formulations are described in detail in U.S. Pat. No. 6,747,014, which is incorporated herein by reference.

### Liposomal Formulations

There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. As used in the present invention, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composi-

tion to be delivered. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Non-cationic liposomes, although not able to fuse as efficiently with the cell wall, are taken up by macrophages *in vivo*.

In order to traverse intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. Therefore, it is desirable to use a liposome which is highly deformable and able to pass through such fine pores.

Further advantages of liposomes include; liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated drugs in their internal compartments from metabolism and degradation (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size and the aqueous volume of the liposomes.

Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomes start to merge with the cellular membranes and as the merging of the liposome and cell progresses, the liposomal contents are emptied into the cell where the active agent may act.

Liposomal formulations have been the focus of extensive investigation as the mode of delivery for many drugs. There is growing evidence that for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side-effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer a wide variety of drugs, both hydrophilic and hydrophobic, into the skin.

Several reports have detailed the ability of liposomes to deliver agents including high-molecular weight DNA into the skin. Compounds including analgesics, antibodies, hormones and high-molecular weight DNAs have been administered to the skin. The majority of applications resulted in the targeting of the upper epidermis

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged DNA molecules to form a stable complex. The positively charged DNA/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang et al., *Biochem. Biophys. Res. Commun.*, 1987, 147, 980-985).

Liposomes which are pH-sensitive or negatively-charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to deliver DNA encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou et al., *Journal of Controlled Release*, 1992, 19, 269-274).

One major type of liposomal composition includes phospholipids other than naturally-derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylg-

lycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

Several studies have assessed the topical delivery of liposomal drug formulations to the skin. Application of liposomes containing interferon to guinea pig skin resulted in a reduction of skin herpes sores while delivery of interferon via other means (e.g., as a solution or as an emulsion) were ineffective (Weiner et al., *Journal of Drug Targeting*, 1992, 2, 405-410). Further, an additional study tested the efficacy of interferon administered as part of a liposomal formulation to the administration of interferon using an aqueous system, and concluded that the liposomal formulation was superior to aqueous administration (du Plessis et al., *Antiviral Research*, 1992, 18, 259-265).

Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective in facilitating the deposition of cyclosporin-A into different layers of the skin (Hu et al. *S. T. P. Pharma. Sci.*, 1994, 4, 6, 466).

Liposomes also include "sterically stabilized" liposomes, a term which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside  $G_{M1}$ , or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen et al., *FEBS Letters*, 1987, 223, 42; Wu et al., *Cancer Research*, 1993, 53, 3765).

Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos et al. (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside  $G_{M1}$ , galactocerebroside sulfate and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S. Pat. No. 4,837,028 and WO 88/04924, both to Allen et al., disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside  $G_{M1}$  or a galactocerebroside sulfate ester. U.S. Pat. No. 5,543,152 (Webb et al.) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim et al.).

Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto et al. (Bull. Chem. Soc. Jpn., 1980, 53, 2778) described liposomes comprising a nonionic detergent, 2C<sub>1215G</sub>, that contains a PEG moiety. Illum et al. (FEBS Lett., 1984, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (e.g., PEG) are described by Sears (U.S. Pat. Nos. 4,426,330 and 4,534,899). Klivanov et al. (FEBS Lett., 1990, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume et al. (Biochimica et Biophysica Acta, 1990, 1029, 91) extended such observations to other PEG-derivatized phospholipids, e.g., DSPE-PEG, formed from the combination of distearylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle et al. (U.S. Pat. Nos. 5,013,556 and 5,356,633) and Martin et al. (U.S. Pat. No. 5,213,804 and European Patent No. EP 0 496 813 B1). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Pat. No. 5,225,212 (both to Martin et al.) and in WO 94/20073 (Zalipsky et al.). Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi et al.). U.S. Pat. No. 5,540,935 (Miyazaki et al.) and U.S. Pat. No. 5,556,948 (Tagawa et al.) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

A number of liposomes comprising nucleic acids are known in the art. WO 96/40062 to Thierry et al. discloses methods for encapsulating high molecular weight nucleic acids in liposomes. U.S. Pat. No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include a dsRNA. U.S. Pat. No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in liposomes. WO 97/04787 to Love et al. discloses liposomes comprising dsRNAs targeted to the raf gene.

Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes may be described as lipid droplets which are so highly deformable that they are easily able to penetrate through pores which are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, e.g., they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines and phosphatides.

The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, N.Y., 1988, p. 285).

#### Nucleic Acid Lipid Particles

In one embodiment, a BCL11A or a KLF1 dsRNA featured in the invention is fully encapsulated in the lipid formulation, e.g., to form a SPLP, pSPLP, SNALP, or other nucleic acid-lipid particle. As used herein, the term "SNALP" refers to a stable nucleic acid-lipid particle, including SPLP. As used herein, the term "SPLP" refers to a nucleic acid-lipid particle comprising plasmid DNA encapsulated within a lipid vesicle. SNALPs and SPLPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (e.g., a PEG-lipid conjugate). SNALPs and SPLPs are extremely useful for systemic applications, as they exhibit extended circulation lifetimes following intravenous (i.v.) injection and accumulate at distal sites (e.g., sites physically separated from the administration site). SPLPs include

"pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in PCT Publication No. WO 00/03683. The particles of the present invention typically have a mean diameter of about 50 nm to about 150 nm, more typically about 60 nm to about 130 nm, more typically about 70 nm to about 110 nm, most typically about 70 nm to about 90 nm, and are substantially nontoxic. In addition, the nucleic acids when present in the nucleic acid-lipid particles of the present invention are resistant in aqueous solution to degradation with a nuclease. Nucleic acid-lipid particles and their method of preparation are disclosed in, e.g., U.S. Pat. Nos. 5,976,567; 5,981,501; 6,534,484; 6,586,410; 6,815,432; and PCT Publication No. WO 96/40964.

In one embodiment, the lipid to drug ratio (mass/mass ratio) (e.g., lipid to dsRNA ratio) will be in the range of from about 1:1 to about 50:1, from about 1:1 to about 25:1, from about 3:1 to about 15:1, from about 4:1 to about 10:1, from about 5:1 to about 9:1, or about 6:1 to about 9:1.

The cationic lipid may be, for example, N,N-dioleoyl-N,N-dimethylammonium chloride (DODAC), N,N-distearoyl-N,N-dimethylammonium bromide (DDAB), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleoyloxypropylamine (DODMA), 1,2-Dilinoleoyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleoxy-3-(dimethylamino)acetoxyp propane (DLin-DAC), 1,2-Dilinoleoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleoyloxy-3-dimethylaminopropane (DLin-2-DMA), 1,2-Dilinoleoyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleoyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleoxylo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)—N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyldidodecan-2-ol (Tech G1), or a mixture thereof. The cationic lipid may comprise from about 20 mol % to about 50 mol % or about 40 mol % of the total lipid present in the particle.

In another embodiment, the compound 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane can be used to prepare lipid-siRNA nanoparticles. Synthesis of 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane is described in U.S. provisional patent application No. 61/107,998 filed on Oct. 23, 2008, which is herein incorporated by reference.

In one embodiment, the lipid-siRNA particle includes 40% 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane: 10%

DSPC: 40% Cholesterol: 10% PEG-C-DOMG (mole percent) with a particle size of  $63.0 \pm 20$  nm and a 0.027 siRNA/Lipid Ratio.

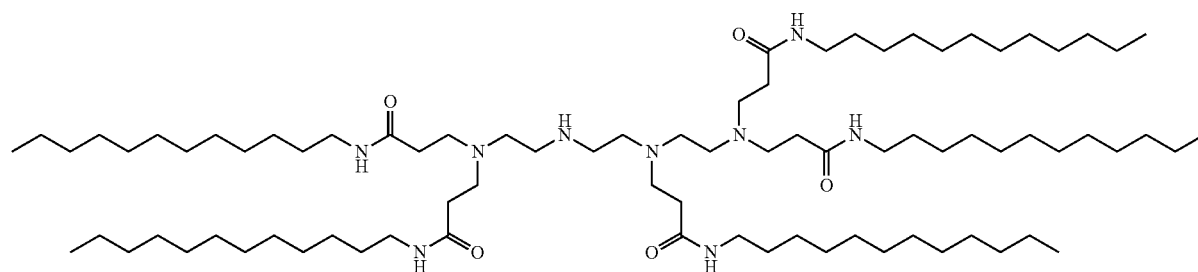
The non-cationic lipid may be an anionic lipid or a neutral lipid including, but not limited to, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl phosphatidylethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidylethanolamine (DSPE), 16-O-monomethyl PE, 16-O-dimethyl PE, 18-1-trans PE, 1-stearoyl-2-oleoyl-phosphatidylethanolamine (SOPE), cholesterol, or a mixture thereof. The non-cationic lipid may be from about 5 mol % to about 90 mol %, about 10 mol %, or about 58 mol % if cholesterol is included, of the total lipid present in the particle.

The conjugated lipid that inhibits aggregation of particles may be, for example, a polyethyleneglycol (PEG)-lipid including, without limitation, a PEG-diacylglycerol (DAG), a PEG-dialkylxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof. The PEG-DAA conjugate may be, for example, a PEG-dilauryloxypropyl ( $C_{12}$ ), a PEG-dimyristyloxypropyl ( $C_{14}$ ), a PEG-dipalmitoyloxypropyl ( $C_{16}$ ), or a PEG-distearoyloxypropyl ( $C_{18}$ ). The conjugated lipid that prevents aggregation of particles may be from 0 mol % to about 20 mol % or about 2 mol % of the total lipid present in the particle.

In some embodiments, the nucleic acid-lipid particle further includes cholesterol at, e.g., about 10 mol % to about 60 mol % or about 48 mol % of the total lipid present in the particle.

#### LNP01

In one embodiment, the lipidoid ND98.4HCl (MW 1487) (see U.S. patent application Ser. No. 12/056,230, filed Mar. 26, 2008, which is herein incorporated by reference), Cholesterol (Sigma-Aldrich), and PEG-Ceramide C16 (Avanti Polar Lipids) can be used to prepare lipid-dsRNA nanoparticles (i.e., LNP01 particles). Stock solutions of each in ethanol can be prepared as follows: ND98, 133 mg/ml; Cholesterol, 25 mg/ml, PEG-Ceramide C16, 100 mg/ml. The ND98, Cholesterol, and PEG-Ceramide C16 stock solutions can then be combined in a, e.g., 42:48:10 molar ratio. The combined lipid solution can be mixed with aqueous dsRNA (e.g., in sodium acetate pH 5) such that the final ethanol concentration is about 35-45% and the final sodium acetate concentration is about 100-300 mM. Lipid-dsRNA nanoparticles typically form spontaneously upon mixing. Depending on the desired particle size distribution, the resultant nanoparticle mixture can be extruded through a polycarbonate membrane (e.g., 100 nm cut-off) using, for example, a thermobarrel extruder, such as Lipex Extruder (Northern Lipids, Inc). In some cases, the extrusion step can be omitted. Ethanol removal and simultaneous buffer exchange can be accomplished by, for example, dialysis or tangential flow filtration. Buffer can be exchanged with, for example, phosphate buffered saline (PBS) at about pH 7, e.g., about pH 6.9, about pH 7.0, about pH 7.1, about pH 7.2, about pH 7.3, or about pH 7.4.



ND98 Isomer I

LNP01 formulations are described, e.g., in International Application Publication No. WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are as follows:

Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
SNALP 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA~7:1
S-XTC 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DPPC/Cholesterol/PEG-cDMA 57.1/7.1/34.4/1.4 lipid:siRNA~7:1
LNP05 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA~6:1
LNP06 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 57.5/7.5/31.5/3.5 lipid:siRNA~11:1
LNP07 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA~6:1
LNP08 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 60/7.5/31/1.5, lipid:siRNA~11:1
LNP09 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC)	XTC/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP10 (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine (ALN100)	ALN100/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP11 (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3)	MC-3/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP12 1,1'-(2-(4-(2-((2-bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyldidodecan-2-ol (C12-200)	C12-200/DSPC/Cholesterol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA 10:1
LNP13 XTC	XTC/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 33:1
LNP14 MC3	MC3/DSPC/Chol/PEG-DMG 40/15/40/5 Lipid:siRNA: 11:1
LNP15 MC3	MC3/DSPC/Chol/PEG-DSG/GalNAc-PEG-DSG 50/10/35/4.5/0.5 Lipid:siRNA: 11:1
LNP16 MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 7:1

Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
LNP17 MC3	MC3/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP18 MC3	MC3/DSPC/Chol/PEG-DMG 50/10/38.5/1.5 Lipid:siRNA: 12:1
LNP19 MC3	MC3/DSPC/Chol/PEG-DMG 50/10/35/5 Lipid:siRNA: 8:1
LNP20 MC3	MC3/DSPC/Chol/PEG-DPG 50/10/38.5/1.5 Lipid:siRNA: 10:1
LNP21 C12-200	C12-200/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 7:1
LNP22 XTC	XTC/DSPC/Chol/PEG-DSG 50/10/38.5/1.5 Lipid:siRNA: 10:1

DSPC: distearoylphosphatidylcholine

DPPE: dipalmitoylphosphatidylethanolamine

PEG-DMG: PEG-dimyristoyl glycerol (C14-PEG, or PEG-C14) (PEG with avg mol wt of 2000)

PEG-DSG: PEG-distyryl glycerol (C18-PEG, or PEG-C18) (PEG with avg mol wt of 2000)

PEG-cDMA: PEG-carbamoyl-1,2-dimyristyloxypropylamine (PEG with avg mol wt of 2000)

SNALP (1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in International Publication No. WO2009/127060, filed Apr. 15, 2009, which is hereby incorporated by reference. XTC comprising formulations are described, e.g., in U.S. Provisional Ser. No. 61/148,366, filed Jan. 29, 2009; U.S. Provisional Ser. No. 61/156,851, filed Mar. 2, 2009; U.S. Provisional Ser. No. 61/175,770, filed May 5, 2009; U.S. Provisional Ser. No. 61/228,373, filed Jul. 24, 2009; U.S. Provisional Ser. No. 61/239,686, filed Sep. 3, 2009, and International Application No. PCT/US2010/022614, filed Jan. 29, 2010, which are hereby incorporated by reference.

MC3 comprising formulations are described, e.g., in U.S. Provisional Ser. No. 61/244,834, filed Sep. 22, 2009; U.S. Provisional Ser. No. 61/185,800, filed Jun. 10, 2009, and International Application No. PCT/US10/28224, filed Jun. 10, 2010, which are hereby incorporated by reference.

ALNY-100 comprising formulations are described, e.g., International patent application number PCT/US09/63933, filed on Nov. 10, 2009, which is hereby incorporated by reference.

C12-200 comprising formulations are described in U.S. Provisional Ser. No. 61/175,770, filed May 5, 2009 and International Application No. PCT/US10/33777, filed May 5, 2010, which are hereby incorporated by reference.

### Synthesis of Cationic Lipids.

Any of the compounds, e.g., cationic lipids and the like, used in the nucleic acid-lipid particles featured in the invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples. All substituents are as defined below unless indicated otherwise.

“Alkyl” means a straight chain or branched, noncyclic or cyclic, saturated aliphatic hydrocarbon containing from 1 to 24 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like.

“Alkenyl” means an alkyl, as defined above, containing at least one double bond between adjacent carbon atoms. Alkenyls include both cis and trans isomers. Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like.

“Alkynyl” means any alkyl or alkenyl, as defined above, which additionally contains at least one triple bond between adjacent carbons. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 3-methyl-1-butyne, and the like.

“Acyl” means any alkyl, alkenyl, or alkynyl wherein the carbon at the point of attachment is substituted with an oxo

group, as defined below. For example, —C(=O)alkyl, —C(=O)alkenyl, and —C(=O)alkynyl are acyl groups.

“Heterocycle” means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 or 2 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined below. Heterocycles include morpholinyl, pyrrolidinyl, pyrrolidinyl, piperidinyl, piperizynyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

The terms “optionally substituted alkyl”, “optionally substituted alkenyl”, “optionally substituted alkynyl”, “optionally substituted acyl”, and “optionally substituted heterocycle” means that, when substituted, at least one hydrogen atom is replaced with a substituent. In the case of an oxo substituent (=O) two hydrogen atoms are replaced. In this regard, substituents include oxo, halogen, heterocycle, —CN, —OR<sup>x</sup>, —NR<sup>x</sup>R<sup>y</sup>, —NR<sup>x</sup>C(=O)R<sup>y</sup>, —NR<sup>x</sup>SO<sub>2</sub>R<sup>y</sup>, —C(=O)R<sup>x</sup>, —C(=O)OR<sup>x</sup>, —C(=O)NR<sup>x</sup>R<sup>y</sup>, —SO<sub>2</sub>R<sup>x</sup> and —SO<sub>2</sub>NR<sup>x</sup>R<sup>y</sup>, wherein n is 0, 1 or 2, R<sup>x</sup> and R<sup>y</sup> are the same or different and independently hydrogen, alkyl or heterocycle, and each of said alkyl and heterocycle substituents may be further substituted with one or more of oxo, halogen,

49

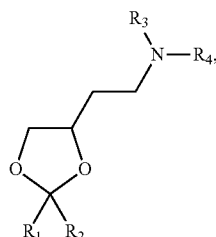
—OH, —CN, alkyl, —OR<sup>x</sup>, heterocycle, —NR<sup>x</sup>R<sup>y</sup>, —NR<sup>x</sup>C(=O)R<sup>y</sup>, —NR<sup>x</sup>SO<sub>2</sub>R<sup>y</sup>, —C(=O)R<sup>x</sup>, —C(=O)OR<sup>x</sup>, —C(=O)NR<sup>x</sup>R<sup>y</sup>, —SO<sub>n</sub>R<sup>x</sup> and —SO<sub>n</sub>NR<sup>x</sup>R<sup>y</sup>.

“Halogen” means fluoro, chloro, bromo and iodo.

In some embodiments, the methods featured in the invention may require the use of protecting groups. Protecting group methodology is well known to those skilled in the art (see, for example, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Green, T. W. et al., Wiley-Interscience, New York City, 1999). Briefly, protecting groups within the context of this invention are any group that reduces or eliminates unwanted reactivity of a functional group. A protecting group can be added to a functional group to mask its reactivity during certain reactions and then removed to reveal the original functional group. In some embodiments an “alcohol protecting group” is used. An “alcohol protecting group” is any group which decreases or eliminates unwanted reactivity of an alcohol functional group. Protecting groups can be added and removed using techniques well known in the art.

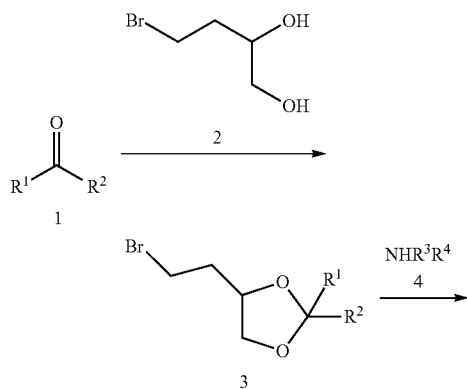
#### Synthesis of Formula A

In one embodiment, nucleic acid-lipid particles featured in the invention are formulated using a cationic lipid of formula A:



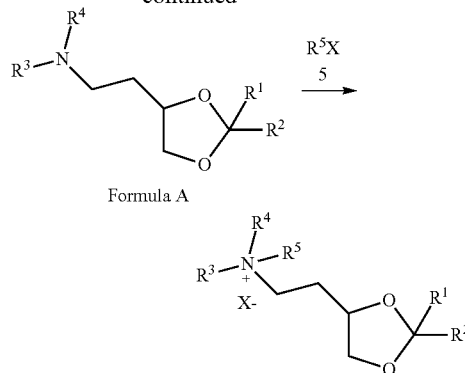
where R1 and R2 are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R3 and R4 are independently lower alkyl or R3 and R4 can be taken together to form an optionally substituted heterocyclic ring. In some embodiments, the cationic lipid is XTC (2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane). In general, the lipid of formula A above may be made by the following Reaction Schemes 1 or 2, wherein all substituents are as defined above unless indicated otherwise.

Scheme 1



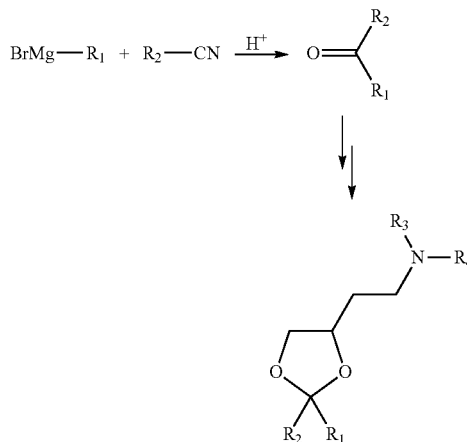
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-continued



Lipid A, where R<sub>1</sub> and R<sub>2</sub> are independently alkyl, alkenyl or alkynyl, each can be optionally substituted, and R<sub>3</sub> and R<sub>4</sub> are independently lower alkyl or R<sub>3</sub> and R<sub>4</sub> can be taken together to form an optionally substituted heterocyclic ring, can be prepared according to Scheme 1. Ketone 1 and bromide 2 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 1 and 2 yields ketal 3. Treatment of ketal 3 with amine 4 yields lipids of formula A. The lipids of formula A can be converted to the corresponding ammonium salt with an organic salt of formula 5, where X is anion counter ion selected from halogen, hydroxide, phosphate, sulfate, or the like.

Scheme 2



Alternatively, the ketone 1 starting material can be prepared according to Scheme 2. Grignard reagent 6 and cyanide 7 can be purchased or prepared according to methods known to those of ordinary skill in the art. Reaction of 6 and 7 yields ketone 1. Conversion of ketone 1 to the corresponding lipids of formula A is as described in Scheme 1.

#### Synthesis of MC3

Preparation of DLin-M-C3-DMA (i.e., (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate) was as follows. A solution of (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-ol (0.53 g), 4-N,N-dimethylaminobutyric acid hydrochloride (0.51 g), 4-N,N-dimethylaminopyridine (0.61 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.53 g) in dichloromethane (5 mL) was stirred at room temperature overnight. The solution was washed with dilute hydrochloric

**51**

acid followed by dilute aqueous sodium bicarbonate. The organic fractions were dried over anhydrous magnesium sulphate, filtered and the solvent removed on a rotovap. The residue was passed down a silica gel column (20 g) using a 1-5% methanol/dichloromethane elution gradient. Fractions 5 containing the purified product were combined and the solvent removed, yielding a colorless oil (0.54 g).

Synthesis of ALNY-100

Synthesis of ketal 519 [ALNY-100] was performed using the following scheme 3:

**52**



55

## Synthesis of 515:

To a stirred suspension of  $\text{LiAlH}_4$  (3.74 g, 0.09852 mol) in 200 mL anhydrous THF in a two neck RBF (1 L), was added a solution of 514 (10 g, 0.04926 mol) in 70 mL of THF slowly at 0° C. under nitrogen atmosphere. After complete addition, reaction mixture was warmed to room temperature and then heated to reflux for 4 h. Progress of the reaction was monitored by TLC. After completion of reaction (by TLC) the mixture was cooled to 0° C. and quenched with careful addition of saturated  $\text{Na}_2\text{SO}_4$  solution. Reaction mixture was stirred for 4 h at room temperature and filtered off. Residue was washed well with THF. The filtrate and washings were mixed and diluted with 400 mL dioxane and 26 mL conc. HCl and stirred for 20 minutes at room temperature. The volatilities were stripped off under vacuum to furnish the hydrochloride salt of 515 as a white solid. Yield: 7.12 g.  $^1\text{H-NMR}$  ( $\text{DMSO}$ , 400 MHz):  $\delta$ =9.34 (broad, 2H), 5.68 (s, 2H), 3.74 (m, 1H), 2.66-2.60 (m, 2H), 2.50-2.45 (m, 5H).

## Synthesis of 516:

To a stirred solution of compound 515 in 100 mL dry DCM in a 250 mL two neck RBF, was added  $\text{NEt}_3$  (37.2 mL, 0.2669 mol) and cooled to 0° C under nitrogen atmosphere. After a slow addition of N-(benzyloxy-carbonyloxy)-succinimide (20 g, 0.08007 mol) in 50 mL dry DCM, reaction mixture was allowed to warm to room temperature. After completion of the reaction (2-3 h by TLC) mixture was washed successively with 1N HCl solution (1×100 mL) and saturated  $\text{NaHCO}_3$  solution (1×50 mL). The organic layer was then dried over anhyd.  $\text{Na}_2\text{SO}_4$  and the solvent was evaporated to give crude material which was purified by silica gel column chromatography to get 516 as sticky mass. Yield: 11 g (89%).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ =7.36-7.27 (m, 5H), 5.69 (s, 2H), 5.12 (s, 2H), 4.96 (br., 1H), 2.74 (s, 3H), 2.60 (m, 2H), 2.30-2.25 (m, 2H). LC-MS  $[\text{M}+\text{H}]^+$ —232.3 (96.94%).

## Synthesis of 517A and 517B:

The cyclopentene 516 (5 g, 0.02164 mol) was dissolved in a solution of 220 mL acetone and water (10:1) in a single neck 500 mL RBF and to it was added N-methyl morpholine-N-oxide (7.6 g, 0.06492 mol) followed by 4.2 mL of 7.6% solution of  $\text{OsO}_4$  (0.275 g, 0.00108 mol) in tert-butanol at room temperature. After completion of the reaction (~3 h), the mixture was quenched with addition of solid  $\text{Na}_2\text{SO}_3$  and resulting mixture was stirred for 1.5 h at room temperature. Reaction mixture was diluted with DCM (300 mL) and washed with water (2×100 mL) followed by saturated  $\text{NaHCO}_3$  (1×50 mL) solution, water (1×30 mL) and finally with brine (1×50 mL). Organic phase was dried over anhyd.  $\text{Na}_2\text{SO}_4$  and solvent was removed in vacuum. Silica gel column chromatographic purification of the crude material was afforded a mixture of diastereomers, which were separated by prep HPLC. Yield: ~6 g crude

517A—Peak-1 (white solid), 5.13 g (96%).  $^1\text{H-NMR}$  ( $\text{DMSO}$ , 400 MHz):  $\delta$ =7.39-7.31 (m, 5H), 5.04 (s, 2H), 4.78-4.73 (m, 1H), 4.48-4.47 (d, 2H), 3.94-3.93 (m, 2H), 2.71 (s, 3H), 1.72-1.67 (m, 4H). LC-MS- $[\text{M}+\text{H}]^+$ —266.3,  $[\text{M}+\text{NH}_4]^+$ —283.5 present, HPLC—97.86%. Stereochemistry confirmed by X-ray.

## Synthesis of 518:

Using a procedure analogous to that described for the synthesis of compound 505, compound 518 (1.2 g, 41%) was obtained as a colorless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$ =7.35-7.33 (m, 4H), 7.30-7.27 (m, 1H), 5.37-5.27 (m, 8H), 5.12 (s, 2H), 4.75 (m, 1H), 4.58-4.57 (m, 2H), 2.78-2.74 (m, 7H), 2.06-2.00 (m, 8H), 1.96-1.91 (m, 2H), 1.62 (m, 4H), 1.48 (m, 2H), 1.37-1.25 (br m, 36H), 0.87 (m, 6H). HPLC—98.65%.

56

## General Procedure for the Synthesis of Compound 519:

A solution of compound 518 (1 eq) in hexane (15 mL) was added in a drop-wise fashion to an ice-cold solution of LAH in THF (1 M, 2 eq). After complete addition, the mixture was heated at 40° C. over 0.5 h then cooled again on an ice bath. The mixture was carefully hydrolyzed with saturated aqueous  $\text{Na}_2\text{SO}_4$  then filtered through celite and reduced to an oil. Column chromatography provided the pure 519 (1.3 g, 68%) which was obtained as a colorless oil.  $^{13}\text{C NMR}$ =130.2, 130.1 (×2), 127.9 (×3), 112.3, 79.3, 64.4, 44.7, 38.3, 35.4, 31.5, 29.9 (×2), 29.7, 29.6 (×2), 29.5 (×3), 29.3 (×2), 27.2 (×3), 25.6, 24.5, 23.3, 22.6, 14.1; Electrospray MS (+ve): Molecular weight for  $\text{C}_{44}\text{H}_{80}\text{NO}_2$  ( $\text{M}+\text{H}$ )<sup>+</sup> Calc. 654.6, Found 654.6.

Formulations prepared by either the standard or extrusion-free method can be characterized in similar manners. For example, formulations are typically characterized by visual inspection. They should be whitish translucent solutions free from aggregates or sediment. Particle size and particle size distribution of lipid-nanoparticles can be measured by light scattering using, for example, a Malvern Zetasizer Nano ZS (Malvern, USA). Particles should be about 20-300 nm, such as 40-100 nm in size. The particle size distribution should be unimodal. The total dsRNA concentration in the formulation, as well as the entrapped fraction, is estimated using a dye exclusion assay. A sample of the formulated dsRNA can be incubated with an RNA-binding dye, such as Ribogreen (Molecular Probes) in the presence or absence of a formulation disrupting surfactant, e.g., 0.5% Triton-X100. The total dsRNA in the formulation can be determined by the signal from the sample containing the surfactant, relative to a standard curve. The entrapped fraction is determined by subtracting the “free” dsRNA content (as measured by the signal in the absence of surfactant) from the total dsRNA content. Percent entrapped dsRNA is typically >85%. For SNALP formulation, the particle size is at least 30 nm, at least 40 nm, at least 50 nm, at least 60 nm, at least 70 nm, at least 80 nm, at least 90 nm, at least 100 nm, at least 110 nm, and at least 120 nm. The suitable range is typically about at least 50 nm to about at least 110 nm, about at least 60 nm to about at least 100 nm, or about at least 80 nm to about at least 90 nm.

Compositions and formulations for oral administration include powders or granules, microparticulates, nanoparticulates, suspensions or solutions in water or non-aqueous media, capsules, gel capsules, sachets, tablets or minitables. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids or binders may be desirable. In some embodiments, oral formulations are those in which dsRNAs featured in the invention are administered in conjunction with one or more penetration enhancers surfactants and chelators. Suitable surfactants include fatty acids and/or esters or salts thereof, bile acids and/or salts thereof. Suitable bile acids/salts include chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA), cholic acid, dehydrocholic acid, deoxycholic acid, glucolic acid, glycholic acid, glycodeoxycholic acid, taurocholic acid, taurodeoxycholic acid, sodium tauro-24,25-dihydro-fusidate and sodium glycodihydrofusidate. Suitable fatty acids include arachidonic acid, undecanoic acid, oleic acid, lauric acid, caprylic acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein, dilaurin, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, an acylcarnitine, an acylcholine, or a monoglyceride, a diglyceride or a pharmaceutically acceptable salt thereof (e.g., sodium). In some embodiments, combinations of penetration enhancers are used, for example, fatty acids/salts in combination with bile acids/salts. One exemplary combination is the sodium

salt of lauric acid, capric acid and UDCA. Further penetration enhancers include polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether. DsRNAs featured in the invention may be delivered orally, in granular form including sprayed dried particles, or complexed to form micro or nanoparticles. DsRNA complexing agents include poly-amino acids; poly-imines; polyacrylates; polyalkylacrylates, polyoxethanes, polyalkylcyanoacrylates; cationized gelatins, albumins, starches, acrylates, polyethyleneglycols (PEG) and starches; polyalkylcyanoacrylates; DEAE-derivatized polyimines, pollulans, celluloses and starches. Suitable complexing agents include chitosan, N-trimethylchitosan, poly-L-lysine, polyhistidine, polyornithine, polyspermines, protamine, polyvinylpyridine, polythiodiethylaminomethylethylene P(TDAE), polyaminostyrene (e.g., p-amino), poly(methylcyanoacrylate), poly(ethylcyanoacrylate), poly(butylcyanoacrylate), poly(isobutylcyanoacrylate), poly(isohexylcyanoacrylate), DEAE-methacrylate, DEAE-hexylacrylate, DEAE-acrylamide, DEAE-albumin and DEAE-dextran, polymethylacrylate, polyhexylacrylate, poly(D,L-lactic acid), poly(DL-lactic-co-glycolic acid (PLGA), alginate, and polyethyleneglycol (PEG). Oral formulations for dsRNAs and their preparation are described in detail in U.S. Pat. No. 6,887,906, US Publ. No. 20030027780, and U.S. Pat. No. 6,747,014, each of which is incorporated herein by reference.

Compositions and formulations for parenteral, intraparenchymal (into the brain), intrathecal, intraventricular or intrahepatic administration may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

The pharmaceutical formulations featured in the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions featured in the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, gel capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

#### Additional Formulations

##### Emulsions

The compositions of the present invention may be prepared and formulated as emulsions. Emulsions are typically heterogeneous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1  $\mu\text{m}$  in diameter (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L. V., Popovich N. G., and Ansel H. C., 2004, Lippincott Williams & Wilkins (8th ed.), New York,

N.Y.; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi et al., in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 301). Emulsions are often biphasic systems comprising two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be of either the water-in-oil (w/o) or the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase, the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase, the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions may contain additional components in addition to the dispersed phases, and the active drug which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed. Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous phase provides an o/w/o emulsion.

Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L. V., Popovich N. G., and Ansel H. C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L. V., Popovich N. G., and Ansel H. C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in

categorizing and selecting surfactants in the preparation of formulations. Surfactants may be classified into different classes based on the nature of the hydrophilic group: non-ionic, anionic, cationic and amphoteric (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y. Rieger, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, nonswelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives and antioxidants (Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed-phase droplets and by increasing the viscosity of the external phase.

Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols and phosphatides that may readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

The application of emulsion formulations via dermatological, oral and parenteral routes and methods for their manufacture have been reviewed in the literature (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery

have been very widely used because of ease of formulation, as well as efficacy from an absorption and bioavailability standpoint (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

In one embodiment of the present invention, the compositions of iRNAs and nucleic acids are formulated as microemulsions. A microemulsion may be defined as a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: Controlled Release of Drugs: Polymers and Aggregate Systems, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 185-215). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails of the surfactant molecules (Schott, in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1985, p. 271).

The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (see e.g., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Allen, L V., Popovich N G., and Ansel H C., 2004, Lippincott Williams & Wilkins (8th ed.), New York, N.Y.; Rosoff, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (SO750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain

alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and tri-glycerides, polyoxyethylated glyceryl fatty acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (see e.g., U.S. Pat. Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (see e.g., U.S. Pat. Nos. 6,191,105; 7,063,860; 7,070,802; 7,157,099; Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385; Ho et al., *J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions may form spontaneously when their components are brought together at ambient temperature. This may be particularly advantageous when formulating thermolabile drugs, peptides or iRNAs. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of iRNAs and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of iRNAs and nucleic acids.

Microemulsions of the present invention may also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the iRNAs and nucleic acids of the present invention. Penetration enhancers used in the microemulsions of the present invention may be classified as belonging to one of five broad categories—surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

#### Penetration Enhancers

In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly iRNAs, to the skin of animals. Most drugs are present in solution in both ionized and non-ionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating non-surfactants (see e.g., Malmsten, M. *Surfactants and polymers in drug delivery*, Informa Health Care, New York, N.Y., 2002; Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

**Surfactants:** In connection with the present invention, surfactants (or “surface-active agents”) are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of iRNAs through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (see e.g., Malmsten, M. *Surfactants and polymers in drug delivery*, Informa Health Care, New York, N.Y., 2002; Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92); and perfluorochemical emulsions, such as FC-43. Takahashi et al., *J. Pharm. Pharmacol.*, 1988, 40, 252).

**Fatty Acids:** Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprinate, monoolein (1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C<sub>1-20</sub> alkyl esters thereof (e.g., methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (i.e., oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, etc.) (see e.g., Touitou, E., et al. *Enhancement in Drug Delivery*, CRC Press, Danvers, Mass., 2006; Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; El Hariri et al., *J. Pharm. Pharmacol.*, 1992, 44, 651-654).

**Bile Salts:** The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble vitamins (see e.g., Malmsten, M. *Surfactants and polymers in drug delivery*, Informa Health Care, New York, N.Y., 2002; Brunton, Chapter 38 in: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., Hardman et al. Eds., McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term “bile salts” includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. Suitable bile salts include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucolic acid (sodium glucolate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (see e.g., Malmsten, M. *Surfactants and polymers in drug delivery*, Informa Health Care, New York, N.Y., 2002; Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Swinyard, Chapter 39 In: Remington's *Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990, pages 782-783; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990,

7, 1-33; Yamamoto et al., *J. Pharm. Exp. Ther.*, 1992, 263, 25; Yamashita et al., *J. Pharm. Sci.*, 1990, 79, 579-583).

**Chelating Agents:** Chelating agents, as used in connection with the present invention, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of iRNAs through the mucosa is enhanced. With regards to their use as penetration enhancers in the present invention, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, 1993, 618, 315-339). Suitable chelating agents include but are not limited to disodium ethylenediaminetetraacetate (EDTA), citric acid, salicylates (e.g., sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laurith-9 and N-amino acyl derivatives of  $\beta$ -diketones (enamines) (see e.g., Katdare, A. et al., *Excipient development for pharmaceutical, biotechnology, and drug delivery*, CRC Press, Danvers, Mass., 2006; Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Buur et al., *J. Control Rel.*, 1990, 14, 43-51).

**Non-Chelating Non-Surfactants:** As used herein, non-chelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of iRNAs through the alimentary mucosa (see e.g., Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33). This class of penetration enhancers include, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin and phenylbutazone (Yamashita et al., *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

Agents that enhance uptake of iRNAs at the cellular level may also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi et al, U.S. Pat. No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo et al., PCT Application WO 97/30731), are also known to enhance the cellular uptake of dsRNAs. Examples of commercially available transfection reagents include, for example Lipofectamine™ (Invitrogen; Carlsbad, Calif.), Lipofectamine 2000™ (Invitrogen; Carlsbad, Calif.), 293Fectin™ (Invitrogen; Carlsbad, Calif.), Cellfectin™ (Invitrogen; Carlsbad, Calif.), DMRIE-C™ (Invitrogen; Carlsbad, Calif.), FreeStyle™ MAX (Invitrogen; Carlsbad, Calif.), Lipofectamine™ 2000 CD (Invitrogen; Carlsbad, Calif.), Lipofectamine™ (Invitrogen; Carlsbad, Calif.), RNAiMAX (Invitrogen; Carlsbad, Calif.), Oligofectamine™ (Invitrogen; Carlsbad, Calif.), Optifect™ (Invitrogen; Carlsbad, Calif.), X-tremeGENE Q2 Transfection Reagent (Roche; Grenzacherstrasse, Switzerland), DOTAP Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), DOSPER Liposomal Transfection Reagent (Grenzacherstrasse, Switzerland), or Eugene (Grenzacherstrasse, Switzerland), Transfectam® Reagent (Promega; Madison, Wis.), TransFast™ Transfection Reagent (Promega; Madison, Wis.), Tfx™-20 Reagent (Promega; Madison, Wis.), Tfx™-50 Reagent (Promega; Madison, Wis.), DreamFect™ (OZ Biosciences; Marseille, France), EcoTransfect (OZ Biosciences; Marseille, France), TransPass™ D1 Transfection Reagent (New England Biolabs; Ipswich, Mass., USA), LyoVec™/LipoGen™ (Invitrogen; San Diego, Calif., USA),

PerFectin Transfection Reagent (Genlantis; San Diego, Calif., USA), NeuroPORTER Transfection Reagent (Genlantis; San Diego, Calif., USA), GenePORTER Transfection reagent (Genlantis; San Diego, Calif., USA), GenePORTER 2 Transfection reagent (Genlantis; San Diego, Calif., USA), Cytofectin Transfection Reagent (Genlantis; San Diego, Calif., USA), BaculoPORTER Transfection Reagent (Genlantis; San Diego, Calif., USA), TroganPORTER™ transfection Reagent (Genlantis; San Diego, Calif., USA), RiboFect (Bioline; Taunton, Mass., USA), PlasFect (Bioline; Taunton, Mass., USA), UniFECTOR (B-Bridge International; Mountain View, Calif., USA), SureFECTOR (B-Bridge International; Mountain View, Calif., USA), or HiFect™ (B-Bridge International, Mountain View, Calif., USA), among others.

Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

#### Carriers

Certain compositions of the present invention also incorporate carrier compounds in the formulation. As used herein, "carrier compound" or "carrier" can refer to a nucleic acid, or analog thereof, which is inert (i.e., does not possess biological activity per se) but is recognized as a nucleic acid by in vivo processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate dsRNA in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'-isothiocyano-stilbene-2,2'-disulfonic acid (Miyao et al., *DsRNA Res. Dev.*, 1995, 5, 115-121; Takakura et al., *DsRNA & Nucl. Acid Drug Dev.*, 1996, 6, 177-183).

#### Excipients

In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient may be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g., magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g., starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium lauryl sulphate, etc.).

Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which do not deleteriously react with nucleic acids can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols,

gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Formulations for topical administration of nucleic acids may include sterile and non-sterile aqueous solutions, non-  
5 aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions may also contain buffers, diluents and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration which  
10 do not deleteriously react with nucleic acids can be used.

Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate,  
15 talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

#### Other Components

The compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established  
20 usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various  
25 dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of  
30 the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously  
35 interact with the nucleic acid(s) of the formulation.

Aqueous suspensions may contain substances that increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol and/or dextran. The suspension may also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the invention include (a) one or more iRNA compounds and (b) one or more biologic agents which function by a non-RNAi mechanism. Examples of such biologic agents include agents that interfere with an interaction of BCL11A  
45 and at least one of the BCL11A-binding partners, e.g., at least one of GATA, FOG-1 and a component of a NuRD complex. Other examples of such biologic agents include agents that interfere with an interaction of KLF1 and at least one of the KLF1-binding partners.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population).  
55 The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit high therapeutic indices are typical.

The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of compositions featured in the invention lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage  
65 form employed and the route of administration utilized. For any compound used in the methods featured in the invention,

the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range of the compound or, when appropriate, of the polypeptide product of a target sequence (e.g., achieving a decreased concentration of the polypeptide) that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the iRNAs featured in the invention can be administered in combination with other known agents effective in treatment of pathological processes mediated by BCL11A or KLF1 expression. In any event, the administering physician can adjust the amount and timing of iRNA administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

#### Methods for Treating Diseases Caused by Expression of a BCL11a or a KLF1 Gene

The invention relates in particular to the use of an iRNA targeting BCL11A or KLF1-mediated disorder or disease. For example, an iRNA targeting a BCL11A or KLF1 gene, or a combination thereof, is used for treatment of hemoglobinopathies. In one embodiment, the subject, e.g., the mammal, is at risk of having, or has been diagnosed, with a hemoglobinopathy. As used herein, the term "hemoglobinopathy" means any defect in the structure or function of a hemoglobin of an individual. It includes defects in the primary, secondary, tertiary or quaternary structure of hemoglobin. The defects can be caused by any mutation, such as deletion mutations or substitution mutations in the coding regions of the  $\beta$ -globin gene, or mutations in, or deletions of, the promoters or enhancers of such genes that cause a reduction in the amount of hemoglobin produced as compared to a normal or standard condition. The term further includes any decrease in the amount or effectiveness of hemoglobin, whether normal or abnormal, caused by external factors such as disease, chemotherapy, toxins, poisons, or the like. In one embodiment, the hemoglobinopathy is a  $\beta$ -hemoglobinopathy, and in another embodiment, the hemoglobinopathy is an  $\alpha$ -hemoglobinopathy. In another embodiment, the hemoglobinopathy is a  $\beta$ -thalassemia, a hemoglobin CC or hemoglobin EE disease. In another embodiment, the hemoglobinopathy is a sickle cell disease.

In thalassemias, the bone marrow synthesizes insufficient amounts of a hemoglobin chain; this in turn reduces the production of red blood cells and causes anemia. Either the  $\alpha$  or the  $\beta$  chain may be affected, but  $\beta$  thalassemias are more common; newborn babies are healthy because their bodies still produce HbF, which does not have  $\beta$  chains; during the first few months of life, the bone marrow switches to producing HbA, and symptoms start to appear.

$\beta$ -thalassemias result from mutation with either non-expressing ( $\beta^0$ ) or low expressing ( $\beta^+$ ) alleles.  $\beta$ -thalassemias vary in severity depending on the genotype, and include minor/trait  $\beta$ -thalassemia ( $\beta/\beta^0$  or  $\beta/\beta^+$ ), intermedia  $\beta$ -thalassemia ( $\beta^0/\beta^+$ ), and major  $\beta$ -thalassemia ( $\beta^0/\beta^0$  or  $\beta^+/ \beta^+$ ).

Hemoglobin C results from a mutation in the beta globin gene and is the predominant hemoglobin found in people with hemoglobin C disease ( $\alpha_2\beta^c_2$ ). Hemoglobin C disease (also called hemoglobin CC disease) is relatively benign, producing a mild hemolytic anemia and splenomegaly. Hemoglobin E results from a mutation in the hemoglobin  $\beta$  chain. People

67

with hemoglobin E (also called hemoglobin EE) disease have a mild hemolytic anemia and mild splenomegaly.

Symptoms of  $\beta$ -thalassemias include, e.g., hemolysis, which causes anemia and splenomegaly; ineffective erythropoiesis, which causes bone marrow drive (skeletal changes), hepatosplenomegaly, consumption of haematinics (megaloblastic anemia), and high uric acid in blood; leg ulcers, infections, and complication due to therapy, e.g., iron overload, which causes endocrinopathy, liver fibrosis and cardiac fibrosis. Administration of an iRNA agent that targets BCL11A or KLF1, or a combination thereof, can be effective to treat one or more of these symptoms.

As used herein, "sickle cell disease" includes, but is not limited to, sickle cell anemia (SS), sickle-hemoglobin, C disease (HbSC), sickle  $\beta^+$ -thalassemia (HbS/ $\beta^+$ ), sickle  $\beta^0$ -thalassemia (HbS/ $\beta^0$ ) and SE disease.

Sickle cell disease is a genetic disorder characterized by the presence of hemoglobin S (Hb S), which causes red blood cells to change from their usual biconcave disc shape to a crescent or sickle shape during deoxygenation. The red blood cell resumes a normal configuration, but after repeated cycles of "sickling and unsickling" the red blood cell becomes damaged permanently, and hemolysis occurs. The hemolysis is responsible for the anemia that is the hallmark of sickle cell disease. Symptoms of sickle-cell disease include, e.g., hemolysis, jaundice, cholelithiasis, aplastic crisis, hemolytic crisis, vaso-occlusive disease, which causes dactylitis, autosplenectomy, acute chest syndrome, stroke priapism, renal papillary necrosis, infarctive crisis, sequestration crisis and leg ulcers. Administration of an iRNA agent that targets BCL11A or KLF1, or a combination thereof, can be effective to treat one or more of these symptoms.

The treatment according to the present invention ameliorates one or more symptoms associated with the disorder by increasing the amount of fetal hemoglobin in the individual. Symptoms typically associated with a hemoglobinopathy, include for example, anemia, tissue hypoxia, organ dysfunction, vaso-occlusive crises, abnormal hematocrit values, ineffective erythropoiesis, abnormal reticulocyte (erythrocyte) count, abnormal iron load, the presence of ring sideroblasts, splenomegaly, hepatomegaly, impaired peripheral blood flow, dyspnea, increased hemolysis, jaundice, anemic pain crises, acute chest syndrome, splenic sequestration, priapism, stroke, hand-foot syndrome, and pain such as angina pectoris.

In another aspect, the invention provides a method for increasing fetal hemoglobin levels and/or decreasing  $\gamma$ -globulin levels in a hematopoietic progenitor cell (e.g., an erythroid cell). The method includes contacting a hematopoietic progenitor cell (e.g., an erythroid cell) with an iRNA targeting a BCL11A or KLF1 gene, or a combination thereof, in an amount effective to increase fetal hemoglobin expression, relative to expression prior to such contacting. In one embodiment, the hematopoietic progenitor cell is present in a subject (e.g., a mammal) in need thereof. In other embodiments, the hematopoietic progenitor cell is contacted ex vivo or in vitro, and the cell or its progeny is administered to said subject.

The term "increasing" or "decreasing" fetal hemoglobin levels or " $\gamma$ -globulin levels" is intended to refer to at least 5%, 10%, 20%, 30%, 40%, 50% or more difference (e.g., increase or decrease relative to a reference value, e.g., a reference where no iRNA is added).

"Hematopoietic progenitor cell" as the term is used herein, refers to cells of a stem cell lineage that give rise to all the blood cell types including the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and the lymphoid

68

lineages (T-cells, B-cells, NK-cells). An "erythroid cell" indicates a cell that undergoes erythropoiesis such that upon final differentiation it forms an erythrocyte or red blood cell (RBC). Such cells belong to one of three lineages, erythroid, lymphoid, and myeloid, originating from bone marrow haematopoietic progenitor cells. Upon exposure to specific growth factors and other components of the haematopoietic microenvironment, haematopoietic progenitor cells can mature through a series of intermediate differentiation cellular types, all intermediates of the erythroid lineage, into RBCs. Thus, "erythroid cells" comprise hematopoietic progenitor cells, rubriblasts, prorubricytes, erythroblasts, metarubricytes, reticulocytes, and erythrocytes.

In some embodiment, the hematopoietic progenitor cell has at least one of the cell surface marker characteristic of haematopoietic progenitor cells: CD34+, CD59+, Thyl/CD90+, CD38<sup>lo</sup>-, and c-kit/CD117+. Typically, the hematopoietic progenitor cells express several of these marker. In some embodiment, the hematopoietic progenitor cells of the erythroid lineage have the cell surface marker characteristic of the erythroid lineage: CD71 and Ter119.

In certain embodiments, the iRNA is administered in an amount such that it improves a hemoglobin deficiency. Assays for evaluating of the effects of the iRNA, and optimizing delivery of iRNA, to modulating bone marrow erythropoiesis and extramedullary erythropoiesis are describes in the Examples below. In certain embodiments, the iRNA is administered such that it targets erythrocyte or erythroid progenitors. Assays for evaluating such effects can include evaluating fetal (embryonic)/adult Hb ratio in bone marrow using an iRNA against KLF1 and/or BCL11a. Additional assays can include the evaluation of iRNA delivery to extramedullary sites. In such assays, the fetal (embryonic)/adult Hb ratio in the liver and spleen can be measured in anemia and/or SCD models.

The invention further relates to the use of an iRNA or a pharmaceutical composition thereof, e.g., for treating a hemoglobinopathy, in combination with other pharmaceuticals and/or other therapeutic methods, e.g., with known pharmaceuticals and/or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. In one embodiment, the iRNA or pharmaceutical composition thereof can be administered in conjunction with one or more inducers of fetal hemoglobin (e.g., 5-azacytidine, hydroxyurea, sodium phenylbutyrate, etc) (see e.g., Perrine et al., *Hematology Am Soc. Hematol. Educ. Program* 2005:38-44), which is hereby incorporated by reference in its entirety).

Exemplary agents and treatment modalities that can be used in combination with an iRNA agent that targets BCL11A or KLF1, or a combination thereof, include one or more of: hydroxyuria (hydroxycarbamide), erythropoietin, 5-azacytidine, butyric acid and analogs thereof (e.g.,  $\gamma$ -aminobutyric acid, phenylbutyrate, valproic acid), phenylacetic and phenylalkyl acids analogs, iron chelators (e.g., to bind excess iron), antibiotics and antivirals, blood transfusions (e.g., red blood cell transfusion) and bone marrow transplants (e.g., stem cell/bone marrow transplants), or a combination thereof.

For example, the iRNAs (or pharmaceutical composition thereof) featured in the invention can be used in combination with hydroxyuria and/or erythropoietin to treat sickle-cell disease. Hydroxyuria and erythropoietin can stimulate the bone marrow to produce more fetal hemoglobin, HbF. HbF can transport oxygen but does not polymerize, so the red blood cells cannot sickle. Thus, these drugs can prevent vaso-occlusive crises.

$\gamma$ -aminobutyric acid can act as a fetal hemoglobin inducer (Perrine et al., *Biochem Biophys Res Commun.* 148(2):694-700 (1987)). Subsequent studies showed that butyrate stimulated globin production in adult baboons (Constantoulakis et al., *Blood*, December; 72(6): 1961-7 (1988)), and it induced  $\gamma$ -globin in erythroid progenitors in adult animals or patients with sickle cell anemia (Perrine et al., *Blood*, 74(1):454-9 (1989)). Derivatives of short chain fatty acids such as phenylbutyrate (Dover et al., *Br J Haematol.* 88(3):555-61 (1994)) and valproic acid (Liakopoulou et al., 1: *Blood*, 186(8):3227-35 (1995)) also have been shown to induce HbF in vivo. Given the large number of short chain fatty acid analogs or derivatives of this family, there are a number of potential compounds of this family more potent than butyrate. Phenylacetic and phenylalkyl acids (Torkelson et al., *Blood Cells Mol Dis.* 22(2): 150-8. (1996)), which were discovered during subsequent studies, were considered potential HbF inducers as they belonged to this family of compounds.

Identifying natural regulators of HbF induction and production could provide a means to devise therapeutic interventions that overcome the various drawbacks of therapies currently available. Recent genome-wide association studies have yielded insights into the genetic basis of numerous complex diseases and traits (McCarthy et al., *Nat Rev Genet* 9, 356 (2008) and Manolio et al. *J Clin Invest* 118, 1590 (2008)). Two genome-wide association studies have identified three major loci containing a set of five common single nucleotide polymorphisms (SNPs) that account for ~20% of the variation in HbF levels (Lettre et al., *Proc Natl Acad Sci USA* (2008); Uda et al., *Proc Natl Acad Sci USA* 105, 1620 (2008); Menzel et al., *Nat Genet* 39, 1197 (2007)). Moreover, several of these variants appear to predict the clinical severity of sickle cell disease (Lettre et al., *Proc Natl Acad Sci USA* (2008)) and at least one of these SNPs may also affect clinical outcome in  $\beta$ -thalassemia (Uda et al., *Proc Natl Acad Sci USA* 105, 1620 (2008)). The SNP with the largest effect size, explaining over 10% of the variation in HbF, is located in the second intron of a gene on chromosome 2, BCL11A. Whereas BCL11A has been investigated for its role in lymphocyte development (Liu et al., *Nat Immunol* 4, 525 (2003) and Liu et al., *Mol Cancer* 5, 18 (2006)), its role in red blood cell production or globin gene regulation has not been previously assessed. The results of recent genetic association studies provide candidate genes to interrogate for their involvement in control of the  $\gamma$ -globin genes, such as BCL11A and KLF1.

Efficacy of treatment or amelioration of disease can be assessed, for example by detection of amelioration of the symptoms of the hemoglobinopathy, slow the course of hemoglobinopathy disease progression, slow or inhibit a symptom of a hemoglobinopathy, slow or inhibit the establishment of secondary symptoms of a hemoglobinopathy or inhibit the development of a secondary symptom of a hemoglobinopathy. The effective amount for the treatment of the hemoglobinopathy depends on the type of hemoglobinopathy to be treated, the severity of the symptoms, the subject being treated, the age and general condition of the subject, the mode of administration and so forth. For any given case, an appropriate "effective amount" can be determined by one of ordinary skill in the art using routine experimentation. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an iRNA targeting KLF1 or BCL11A or pharmaceutical composition thereof, "effective against" a hemoglobinopathy indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such

as an improvement of symptoms, a cure, a reduction in disease load, reduction in tumor mass or cell numbers, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of cancer.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, e.g., at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given iRNA drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

The iRNA and an additional therapeutic agent can be administered in combination in the same composition, e.g., parenterally, or the additional therapeutic agent can be administered as part of a separate composition or by another method described herein.

Patients can be administered a therapeutic amount of iRNA, such as 0.5 mg/kg, 1.0 mg/kg, 1.5 mg/kg, 2.0 mg/kg, or 2.5 mg/kg dsRNA. The iRNA can be administered by intravenous infusion over a period of time, such as over a 5 minute, 10 minute, 15 minute, 20 minute, or 25 minute period. The administration is repeated, for example, on a regular basis, such as biweekly (i.e., every two weeks) for one month, two months, three months, four months or longer. After an initial treatment regimen, the treatments can be administered on a less frequent basis. For example, after administration biweekly for three months, administration can be repeated once per month, for six months or a year or longer. Administration of the iRNA can reduce BCL11A or KLF1 levels, e.g., in a cell, tissue, blood, urine or other compartment of the patient by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% or at least 90% or more.

Before administration of a full dose of the iRNA, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction, or for elevated lipid levels or blood pressure. In another example, the patient can be monitored for unwanted effects.

#### Methods for Modulating Expression of a KLF1 or BCL11a Gene

In yet another aspect, the invention provides a method for modulating (e.g., inhibiting or activating) the expression of a KLF1 or BCL11A gene in a mammal.

In one embodiment, the method includes administering a composition described herein, e.g., a composition comprising an iRNA that targets KLF1 or BCL11A, to the mammal such that expression of the target KLF1 or BCL11A gene is decreased, such as for an extended duration, e.g., at least two, three, four days or more, e.g., one week, two weeks, three weeks, or four weeks or longer.

In another embodiment, the method includes administering a composition as described herein to a mammal such that expression of the target KLF1 or BCL11A gene is increased by e.g., at least 10% compared to an untreated animal. In some embodiments, the activation of KLF1 or BCL11A occurs over an extended duration, e.g., at least two, three, four days or more, e.g., one week, two weeks, three weeks, four weeks, or more. Without wishing to be bound by theory, an iRNA can activate KLF1 or BCL11A expression by stabiliz-

ing the KLF1 or BCL11A mRNA transcript, interacting with a promoter in the genome, and/or inhibiting an inhibitor of KLF1 or BCL11A expression.

The iRNAs useful for the methods and compositions featured in the invention specifically target RNAs (primary or processed) of the KLF1 or BCL11A gene. Compositions and methods for inhibiting the expression of these KLF1 or BCL11A genes using iRNAs can be prepared and performed as described elsewhere herein.

In one embodiment, the method includes administering a composition containing an iRNA, where the iRNA includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the KLF1 or BCL11A gene of the mammal to be treated. When the organism to be treated is a mammal such as a human, the composition may be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (e.g., intraventricular, intraparenchymal and intrathecal), intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In certain embodiments, the compositions are administered by intravenous infusion or injection.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the iRNAs and methods featured in the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

## EXAMPLES

### Example 1

#### iRNA Synthesis

##### Source of Reagents

Where the source of a reagent is not specifically given herein, such reagent may be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

##### Oligonucleotide Synthesis.

All oligonucleotides are synthesized on an AKTAoligopilot synthesizer. Commercially available controlled pore glass solid support (dT-CPG, 500 Å, Prime Synthesis) and RNA phosphoramidites with standard protecting groups, 5'-O-dimethoxytrityl N6-benzoyl-2'-t-butyl dimethylsilyl-adenosine-3'-O—N,N'-diisopropyl-2-cyanoethylphosphoramidite, 5'-O-dimethoxytrityl-N4-acetyl-2'-t-butyl dimethylsilyl-cytidine-3'-O—N,N'-diisopropyl-2-cyanoethylphosphoramidite, 5'-O-dimethoxytrityl-N2-isobutyl-2'-t-butyl dimethylsilyl-guanosine-3'-O—N,N'-diisopropyl-2-cyanoethylphosphoramidite, and 5'-O-dimethoxytrityl-2'-t-butyl dimethylsilyl-uridine-3'-O—N,N'-diisopropyl-2-cyanoethylphosphoramidite (Pierce Nucleic Acids Technologies) were used for the oligonucleotide synthesis. The 2'-F phosphoramidites, 5'-O-dimethoxytrityl-N4-acetyl-2'-fluoro-cytidine-3'-O—N,N'-diisopropyl-2-cyanoethylphosphoramidite and 5'-O-dimethoxytrityl-2'-fluoro-uridine-3'-O—N,N'-diisopropyl-2-cyanoethyl-

phosphoramidite are purchased from (Promega). All phosphoramidites are used at a concentration of 0.2M in acetonitrile (CH<sub>3</sub>CN) except for guanosine which is used at 0.2M concentration in 10% THF/ANC (v/v). Coupling/recycling time of 16 minutes is used. The activator is 5-ethyl thiotetrazole (0.75M, American International Chemicals); for the PO-oxidation iodine/water/pyridine is used and for the PS-oxidation PADS (2%) in 2,6-lutidine/ACN (1:1 v/v) is used.

3'-ligand conjugated strands are synthesized using solid support containing the corresponding ligand. For example, the introduction of cholesterol unit in the sequence is performed from a hydroxyprolinol-cholesterol phosphoramidite. Cholesterol is tethered to trans-4-hydroxyprolinol via a 6-aminohexanoate linkage to obtain a hydroxyprolinol-cholesterol moiety. 5'-end Cy-3 and Cy-5.5 (fluorophore) labeled iRNAs are synthesized from the corresponding Quasar-570 (Cy-3) phosphoramidite are purchased from Biosearch Technologies. Conjugation of ligands to 5'-end and or internal position is achieved by using appropriately protected ligand-phosphoramidite building block. An extended 15 min coupling of 0.1 M solution of phosphoramidite in anhydrous CH<sub>3</sub>CN in the presence of 5-(ethylthio)-1H-tetrazole activator to a solid-support-bound oligonucleotide. Oxidation of the internucleotide phosphite to the phosphate is carried out using standard iodine-water as reported (1) or by treatment with tert-butyl hydroperoxide/acetonitrile/water (10:87:3) with 10 min oxidation wait time conjugated oligonucleotide. Phosphorothioate is introduced by the oxidation of phosphite to phosphorothioate by using a sulfur transfer reagent such as DDTT (purchased from AM Chemicals), PADS and or Beaucage reagent. The cholesterol phosphoramidite is synthesized in house and used at a concentration of 0.1 M in dichloromethane. Coupling time for the cholesterol phosphoramidite is 16 minutes.

##### Deprotection I (Nucleobase Deprotection)

After completion of synthesis, the support is transferred to a 100 mL glass bottle (VWR). The oligonucleotide is cleaved from the support with simultaneous deprotection of base and phosphate groups with 80 mL of a mixture of ethanolic ammonia [ammonia:ethanol (3:1)] for 6.5 h at 55° C. The bottle is cooled briefly on ice and then the ethanolic ammonia mixture is filtered into a new 250-mL bottle. The CPG is washed with 2×40 mL portions of ethanol/water (1:1 v/v). The volume of the mixture is then reduced to ~30 mL by roto-vap. The mixture is then frozen on dry ice and dried under vacuum on a speed vac.

##### Deprotection II (Removal of 2'-TBDMS Group)

The dried residue is resuspended in 26 mL of triethylamine, triethylamine trihydrofluoride (TEA.3HF) or pyridine-HF and DMSO (3:4:6) and heated at 60° C. for 90 minutes to remove the tert-butyl dimethylsilyl (TBDMS) groups at the 2' position. The reaction is then quenched with 50 mL of 20 mM sodium acetate and the pH is adjusted to 6.5. Oligonucleotide is stored in a freezer until purification.

##### Analysis

The oligonucleotides are analyzed by high-performance liquid chromatography (HPLC) prior to purification and selection of buffer and column depends on nature of the sequence and or conjugated ligand.

##### HPLC Purification

The ligand-conjugated oligonucleotides are purified by reverse-phase preparative HPLC. The unconjugated oligonucleotides are purified by anion-exchange HPLC on a TSK gel column packed in house. The buffers are 20 mM sodium phosphate (pH 8.5) in 10% CH<sub>3</sub>CN (buffer A) and 20 mM sodium phosphate (pH 8.5) in 10% CH<sub>3</sub>CN, 1M NaBr (buffer

B). Fractions containing full-length oligonucleotides are pooled, desalted, and lyophilized. Approximately 0.15 OD of desalted oligonucleotides are diluted in water to 150  $\mu$ L and then pipetted into special vials for CGE and LC/MS analysis. Compounds are then analyzed by LC-ESMS and CGE.

#### iRNA Preparation

For the general preparation of iRNA, equimolar amounts of sense and antisense strand are heated in 1 $\times$ PBS at 95° C. for 5 min and slowly cooled to room temperature. Integrity of the duplex is confirmed by HPLC analysis.

Nucleic acid sequences are represented below using standard nomenclature, and specifically the abbreviations of Table 1.

TABLE 1

Abbreviations of nucleotide monomers used in nucleic acid sequence representation. It will be understood that these monomers, when present in an oligonucleotide, are mutually linked by 5'-3'-phosphodiester bonds.	
Abbreviation	Nucleotide(s)
A	adenosine
C	cytidine
G	guanosine
T	thymidine
U	uridine
N	any nucleotide (G, A, C, T or U)
a	2'-O-methyladenosine
c	2'-O-methylcytidine
g	2'-O-methylguanosine
u	2'-O-methyluridine
dT	2'-deoxythymidine
s	phosphorothioate linkage

#### Example 2

##### KLF1 or BCL11A siRNA Design and Synthesis

#### Transcripts

Oligonucleotide design for KLF1 siRNAs was carried out to identify siRNAs targeting the gene encoding the human “KLF1 molecule” and the orthologous sequences from mice (*Mus musculus*). The design process used the KLF1 transcripts NM\_006563.3, SEQ ID NO: 1 (human) or NM\_010635.2 (GI:225543579), SEQ ID NO: 2 (mouse). All sequences were obtained from the NCBI RefSeq collection.

Oligonucleotide design for BCL11A siRNAs was carried out to identify siRNAs targeting the gene encoding the human “BCL11A molecule” (including variants 1, 2 and 3) and the orthologous sequences from mice (*Mus musculus*). The design process used the human BCL11A variant 1 mRNA (Ref. Seq. NM\_022893.3 (GI:148539885), SEQ ID NO: 3); human BCL11A variant 2 mRNA (Ref. Seq. NM\_018014.3 (GI:148539884), SEQ ID NO: 4); human BCL11A variant 3 mRNA (Ref. Seq. NM\_018014.3 (GI:20336312), SEQ ID NO: 5); mouse BCL11A variant 1 mRNA (Ref. Seq. NM\_016707.3 (GI:226530130), SEQ ID NO: 6); mouse BCL11A variant 2 mRNA (Ref. Seq. NM\_016707.3 (GI:226530130), SEQ ID NO: 7); and mouse BCL11A variant 3 mRNA (Ref. Seq. NM\_001159290.1 (GI:226530196), SEQ ID NO: 8).

Sense and antisense human and mouse KLF1 or human BCL11A (variants 1, 2 and 3) derived siRNA oligos were synthesized. The oligos are presented in Table 2A-1, 2A-2, 2A-3, Table 2B and 2C.

#### siRNA Design and Specificity Prediction

The specificity of the 19mer oligo sets was predicted from each sequence. The KLF1 or BCL11A siRNAs were used in

a comprehensive search against their respective human, or mouse and rat transcriptomes (defined as the set of NM\_ and XM\_ records within the NCBI Refseq set) using the FASTA algorithm. The Python script ‘offtargetFasta.py’ was then used to parse the alignments and generate a score based on the position and number of mismatches between the siRNA and any potential ‘off-target’ transcript. The off-target score is weighted to emphasize differences in the ‘seed’ region of siRNAs, in positions 2-9 from the 5' end of the molecule. The off-target score is calculated as follows: mismatches between the oligo and the transcript are given penalties. A mismatch in the seed region in positions 2-9 of the oligo is given a penalty of 2.8; mismatches in the putative cleavage sites 10 and 11 are given a penalty of 1.2, and all other mismatches a penalty of 1. The off-target score for each oligo-transcript pair is then calculated by summing the mismatch penalties. The lowest off-target score from all the oligo-transcript pairs is then determined and used in subsequent sorting of oligos. Both siRNAs strands were assigned to a category of specificity according to the calculated scores: a score above 3 qualifies as highly specific, equal to 3 as specific and between 2.2 and 2.8 as moderate specific. In picking which oligos to synthesize, we sorted from high to low by the off-target score of the antisense strand and took the best (lowest off-target score) oligo pairs.

#### Synthesis of KLF1 or BCL11A Sequences

KLF1 or BCL11A sequences can be synthesized on a MerMade 192 synthesizer at 1  $\mu$ mol scale.

For all the sequences in the list, ‘endolight’ chemistry was applied as detailed below.

All pyrimidines (cytosine and uridine) in the sense strand contained 2'-O-Methyl bases (2' O-Methyl C and 2'-O-Methyl U)

In the antisense strand, pyrimidines adjacent to (towards 5' position) ribo A nucleoside were replaced with their corresponding 2-O-Methyl nucleosides

A two base dTsdT extension at 3' end of both sense and antisense sequences was introduced

The sequence file was converted to a text file to make it compatible for loading in the MerMade 192 synthesis software

#### Synthesis, Cleavage and Deprotection:

The synthesis of KLF1 or BCL11A sequences can use solid supported oligonucleotide synthesis using phosphoramidite chemistry.

The synthesis of the above sequences can be performed at 1  $\mu$ m scale in 96 well plates. The amidite solutions are prepared at 0.1M concentration and ethyl thio tetrazole (0.6M in Acetonitrile) is used as activator.

The synthesized sequences can be cleaved and deprotected in 96 well plates, using methylamine in the first step and fluoride reagent in the second step. The crude sequences can be precipitated using acetone:ethanol (80:20) mix and the pellet can be re-suspended in 0.02M sodium acetate buffer. Samples from each sequence can be analyzed by LC-MS to confirm the identity, UV for quantification and a selected set of samples by IEX chromatography to determine purity.

#### Purification and Desalting:

KLF1 or BCL11A sequences can be purified on AKTA explorer purification system using Source 15Q column. A column temperature of 65C is maintained during purification. Sample injection and collection is performed in 96 well (1.8 mL-deep well) plates. A single peak corresponding to the full length sequence is collected in the eluent. The purified sequences are desalted on a Sephadex G25 column using AKTA purifier. The desalted KLF1 or BCL11A sequences are

75

analyzed for concentration (by UV measurement at A260) and purity (by ion exchange HPLC). The single strands are then submitted for annealing.

In vitro Screening:

Cell Culture and Transfections:

RKO or Hep3B (ATCC, Manassas, Va.) cells are grown to near confluence at 37° C. in an atmosphere of 5% CO<sub>2</sub> in McCoy's or EMEM (respectively) (ATCC) supplemented with 10% FBS, streptomycin, and glutamine (ATCC) before being released from the plate by trypsinization. Reverse transfection is carried out by adding 5 µl of Opti-MEM to 5 µl of siRNA duplexes per well into a 96-well plate along with 10 µl of Opti-MEM plus 0.2 µl of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad Calif. cat #13778-150) and incubated at room temperature for 15 minutes. 80 µl of complete growth media without antibiotic containing 2.0 × 10<sup>4</sup> HeLa cells are then added. Cells are incubated for 24 hours prior to RNA purification. Experiments were performed at 0.1 or 10 nM final duplex concentration for single dose screens with each of the BCL11A or KLF1 duplexes.

Total RNA Isolation Using MagMAX-96 Total RNA Isolation Kit (Applied Biosystem, Foster City Calif., Part #: AM1830):

Cells are harvested and lysed in 140 µl of Lysis/Binding Solution then mixed for 1 minute at 850 rpm using and Eppendorf Thermomixer (the mixing speed was the same throughout the process). Twenty micro liters of magnetic beads and Lysis/Binding Enhancer mixture were added into cell-lysate and mixed for 5 minutes. Magnetic beads are captured using magnetic stand and the supernatant was removed without disturbing the beads. After removing supernatant, magnetic beads are washed with Wash Solution 1 (isopropanol added) and mixed for 1 minute. Beads are capture again and supernatant removed. Beads are then washed with 150 µl Wash Solution 2 (Ethanol added), captured and supernatant was removed. 50 ul of DNase mixture (MagMax turbo DNase

76

Buffer and Turbo DNase) is then added to the beads and they are mixed for 10 to 15 minutes. After mixing, 100 µl of RNA Rebinding Solution is added and mixed for 3 minutes. Supernatant was removed and magnetic beads are washed again with 150 µl Wash Solution 2 and mixed for 1 minute and supernatant is removed completely. The magnetic beads were mixed for 2 minutes to dry before RNA was eluted with 50 µl of water.

cDNA Synthesis Using ABI High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, Calif., Cat #4368813):

A master mix of 2 µl 10× Buffer, 0.8 µl 25× dNTPs, 2 µl Random primers, 1 µl Reverse Transcriptase, 1 µl RNase inhibitor and 3.2 µl of H<sub>2</sub>O per reaction were added into 10 µl total RNA. cDNA is generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, Calif.) through the following steps: 25° C. 10 min, 37° C. 120 min, 85° C. 5 sec, 4° C. hold.

Real Time PCR:

2 µl of cDNA were added to a master mix containing 0.5 µl GAPDH TaqMan Probe (Applied Biosystems Cat #4326317E), 0.5 µl BCL11A or a KLF1 TaqMan probe (Applied Biosystems cat #Hs01125301\_m1) and 5 µl Roche Probes Master Mix (Roche Cat #04887301001) in a total of 10 µl per well in a LightCycler 480 384 well plate (Roche cat #0472974001). Real time PCR was done in a LightCycler 480 Real Time PCR machine (Roche). Each duplex was tested in at least two independent transfections. For those siRNAs that were tested in RKO and Hep3B cells, at least three transfections are performed. Each transfection is assayed by qPCR in duplicate.

Real time data were analyzed using the ΔΔCt method. Each sample was normalized to GAPDH expression and knock-down was assessed relative to cells transfected with the non-targeting duplex AD-1955. IC50s were defined using a 4 parameter fit model in XLfit.

TABLE 2A-1

Human KLF1 Single Strands and Duplex Sequences				
SEQ ID NO: (sense)	Position of 5' base on transcript NM_006563.3 sense (5'-3')	antisense (5'-3')	SEQ ID NO: (antisense)	
9	149	AGUGGUGGCGCUCGCAAGA	UCUUCGAGCGCCACCACU	10
11	210	GCCCCUCCACGUGAAGUCU	AGACUUCACGUGGAGGGGC	12
13	393	CGAGACUCUGGGCGCAUUA	AUAUGCGCCAGAGUCUCG	14
15	440	UUUUGGGUUCGGAGGAUCA	UGAUCCUCCGAACCCAAAA	16
17	448	UCGGAGGAUACUCGGGUU	AACCCGAGUGAUCCUCCGA	18
19	554	UGGCGCUGCAACCGGUGUA	UACACCGGUUGCAGCGCCA	20
21	761	CCUCCUUCUGAGUUGUUU	AAACAACUCAGGAAGGAGG	22
23	856	AAGCGAGGCCGACGUUCGU	ACGAACGUCGGCCUCGCUU	24
25	1088	AGCUCUGCCACGUGCUUU	AAAGCACGUGGGCAGAGCU	26
27	1158	GCCCUGGCACUUGGACUCU	AGAGUCCAAGUGCCAGGGC	28
29	1162	UGGCACUUGGACUCUCCUA	UAGGAGAGUCCAAGUGCCA	30
31	1174	UCUCCUAGUGACUGGGGAU	AUCCCCAGUCACUAGGAGA	32
33	1251	UGGUUUUCCACGAAUGGA	UCCAUUCGUGGAAAACCA	34

TABLE 2A-1 -continued

Human KLFL Single Strands and Duplex Sequences				
SEQ ID NO: (sense)	Position of 5' base on transcript NM_006563.3 sense (5'-3')	antisense (5'-3')	SEQ ID NO: (antisense)	
35	1255	UUUCCACGAAUGGACCCU	AGGGUCCAUCGUGGGAAA	36
37	1277	CUGGACUCGCGUCCCAA	UUUGGAACGCGAGUCCAG	38
39	1292	CAAAGAUCCACCCAAUAU	AUAUUUGGUGGAUCUUUG	40
41	1308	UAUCAAAACGACCCAU	UAUGGGUCCGUGUUUGAUA	41
43	1345	UCUUACGGAAAAUCCGACA	UGUCGGAUUUCCGUAAGA	44
45	1346	CUUACGGAAAAUCCGACAA	UUGUCGGAUUUCCGUAAG	46
47	1350	CGGAAAAUCCGACAAGCCU	AGGCUUGUCGGAUUUCCG	48
49	1351	GGAAAAUCCGACAAGCCUU	AAGGCUUGUCGGAUUUCC	50
51	1390	GAGAUGUCCAAACUGUCGU	ACGACAGUUUGGACAUCUC	52
53	1393	AUGUCCAAACUGUCGUGCA	UGCACGACAGUUUGGACAU	54
55	1394	UGUCCAAACUGUCGUGCAA	UUGCACGACAGUUUGGACA	56
57	1395	GUCCAAACUGUCGUGCAAA	UUUGCACGACAGUUUGGAC	58
59	1399	AAACUGUCGUGCAAAACCA	UGGGUUUGCACGACAGUUU	60
61	1407	GUGCAAACCCAGUGAGACA	UGUCUCACUGGGUUUGCAC	62
63	1419	UGAGACAGACCGCCAAUA	UAUUUGGCGGUCUGUCUA	64
65	1420	GAGACAGACCGCCAAUAA	UUAUUUGGCGGUCUGUCUC	66
67	1421	AGACAGACCGCCAAUAAA	UUUAUUUGGCGGUCUGUCU	68
69	1425	AGACCGCCAAUAAACGGA	UCCGUUUUUUUGGCGGUCU	70
71	1429	CGCCAAUAAACGGACUCA	UGAGUCCGUUUUUUGGCG	72
73	1434	AAUAAACGGACUCAGUGGA	UCCACUGAGUCCGUUUUUU	74
75	1442	GACUCAGUGGACACUCAGA	UCUGAGUGUCCACUGAGUC	76
77	1521	CUGGGUCUAGAAAGCGGCU	AGCCGCUUUUAGACCCAG	78
79	1537	GCUCUGAAGGUCCCUUAU	AUAAGGGACCUUCAGGAGC	80
81	1538	CUCCUGAAGGUCCCUUAUU	AAUAAGGGACCUUCAGGAG	82
83	1540	CCUGAAGGUCCCUUAUUGU	ACAAUAAGGGACCUUCAGG	84
85	1548	UCCCUUAUUGUGGCUGAUA	UAUCAGCCACAAUAGGGA	86
87	1549	CCCUUAUUGUGGCUGAUAU	AUAUCAGCCACAAUAGGG	88
89	1550	CCUUAUUGUGGCUGAUAUU	AAUAUCAGCCACAAUAGG	90
91	1556	UGUGGCUGAUAUAACUGU	ACAGUUAUAUACAGCCACA	92
93	1575	CAAUGGUUAUGGGUCCUAU	AUAGGACCCAUACCAUUG	94
95	1576	AAUGGUUAUGGGUCCUAUA	UAUAGGACCCAUACCAUU	96
97	1577	AUGGUUAUGGGUCCUAUAA	UUUAUAGGACCCAUACCAU	98
99	1578	UGGUUAUGGGUCCUAUAAA	UUUAUAGGACCCAUACCA	100
101	1579	GGUUAUGGGUCCUAUAAAA	UUUUAUAGGACCCAUACCA	102

TABLE 2A-2

Human KLF1 Unmodified siRNA Duplex Sequences					
Duplex ID	SEQ ID NO.: (sense)	Sense sequence	Position in NM_006563.3	Antisense Sequence	SEQ ID NO.: (antisense)
AD-46099.1	59	AAACUGUCGUGCAAACCCA	1399-1417	UGGGUUUGCACGACAGUUU	60
AD-46132.1	23	AAGCGAGGCCGACGUUCGU	856-874	ACGAACGUCGGCCUCGCUU	24
AD-46094.1	73	AAUAAACGGACUCAGUGGA	1434-1452	UCCACUGAGUCCGUUUUUAU	74
AD-46113.1	95	AAUGGUUAUGGGUCCUAUA	1576-1594	UAUAGGACCCAUAAACCAU	96
AD-46123.1	67	AGACAGACCGCCAAAUAAA	1421-1439	UUUAUUUGGCGGUCUGUCU	68
AD-46129.1	69	AGACCGCCAAAUAAACGGA	1425-1443	UCCGUUUUAUUUGGCGGUCU	70
AD-46091.1	25	AGCUCUGCCACGUGCUUU	1088-1106	AAAGCACGUGGGCAGAGCU	26
AD-46090.1	9	AGUGGUGGCGCUCGGAAGA	149-167	UCUUCGGAGCGCCACCACU	10
AD-46119.1	97	AUGGUUAUGGGUCCUAUAA	1577-1595	UUUAAGGACCCAUAAACAU	98
AD-46128.1	53	AUGUCCAAACUGUCUGCA	1393-1411	UGCACGACAGUUUGGACAU	54
AD-46133.1	39	CAAAGAUCCACCCAAAUAU	1292-1310	AUAUUUGGGUGGAUCUUUG	40
AD-46107.1	93	CAAUGGUUAUGGGUCCUAU	1575-1593	AUAGGACCCAUAAACCAUUG	94
AD-46136.1	87	CCCUUAUUGUGGCUGAUAU	1549-1567	AUAUCAGCCACAAUAAGGG	88
AD-46126.1	21	CCUCCUUCUGAGUUGUUU	761-779	AAACAACUCAGGAAGGAGG	22
AD-46124.1	83	CCUGAAGGUCCCUUAUUGU	1540-1558	ACAAUAAGGGACCUUCAGG	84
AD-46095.1	89	CCUUAUUGUGGCUGAUUU	1550-1568	AAUAUCAGCCACAAUAAGG	90
AD-46095.3	89	CCUUAUUGUGGCUGAUUU	1550-1568	AAUAUCAGCCACAAUAAGG	90
AD-46102.1	13	CGAGACUCUGGGCGCAUAU	393-411	AUAUGCGCCAGAGUCUCG	14
AD-46135.1	71	CGCCAAAUAAACGGACUCA	1429-1447	UGAGUCCGUUUUUUUGGCG	72
AD-46110.1	47	CGGAAAAUCCGACAAGCCU	1350-1368	AGGCUUGUCGGAUUUUCCG	48
AD-46118.1	81	CUCCUGAAGGUCCCUUAUU	1538-1556	AAUAAGGGACCUUCAGGAG	82
AD-46127.1	37	CUGGACUCGCGUUCCTAAA	1277-1295	UUUGGGAACGCGAGUCCAG	38
AD-46106.1	77	CUGGGUCUAGAAAGCGGCU	1521-1539	AGCCGCUUUCUAGACCCAG	78
AD-46104.1	45	CUUACGGAAAAUCCGACAA	1346-1364	UUGUCGGAUUUUCCGUAAG	46
AD-46100.1	75	GACUCAGUGGACACUCAGA	1442-1460	UCUGAGUGUCCACUGAGUC	76
AD-46117.1	65	GAGACAGACCGCCAAAUAA	1420-1438	UUUUUUUGGCGGUCUGUCUC	66
AD-46122.1	51	GAGAUGUCCAAACUGUCGU	1390-1408	ACGACAGUUUGGACAUCUC	52
AD-46096.1	11	GCCCCUCCACGUGAAGUCU	210-228	AGACUUCACGUGGAGGGGC	12
AD-46097.1	27	GCCCUUGGCACUUGGACUCU	1158-1176	AGAGUCCAAGUGCCAGGGC	28
AD-46112.1	79	GCUCUGAAGGUCCCUUAU	1537-1555	AUAAGGGACCUUCAGGAGC	80
AD-46116.1	49	GGAAAAUCCGACAAGCCUU	1351-1369	AAGGCUUGUCGGAUUUUCC	50
AD-46093.1	57	GUCCAAACUGUCGUGCAAA	1395-1413	UUUGCACGACAGUUUGGAC	58
AD-46105.1	61	GUGCAAACCCAGUGAGACA	1407-1425	UGUCUCACUGGGUUUGCAC	62
AD-46092.1	41	UAUCAAAACACGGACCCAU	1308-1326	UAUGGGUCCGUGUUUGAUA	41
AD-46130.1	85	UCCCUUAUUGUGGCUGAUA	1548-1566	UAUCAGCCACAAUAAGGGA	86
AD-53284.1	85	UCCCUUAUUGUGGCUGAUAU	1546-1568	AAUAUCAGCCACAAUAAGGGACC	86
AD-53290.1	85	UCCCUUAUUGUGGCUGAUAU	1546-1568	AAUAUCAGCCACAAUAAGGGACC	86

TABLE 2A-2 -continued

Human KLF1 Unmodified siRNA Duplex Sequences					
Duplex ID	SEQ ID NO.: (sense)	Sense sequence	Position in NM_006563.3	Antisense Sequence	SEQ ID NO.: (antisense)
AD-53295.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53301.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53307.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53308.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53309.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53310.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53311.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53312.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53313.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53314.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53315.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53316.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53317.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53318.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53319.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53320.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53321.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-53322.1	85	UCCCUUAUUGUGGCUGAUUU	1546-1568	AAUAUCAGCCACAUAAGGGACC	86
AD-46114.1	17	UCGGAGGAUCACUCGGGUU	448-466	AACCCGAGUGAUCCUCCGA	18
AD-46109.1	31	UCUCCUAGUGACUGGGGAU	1174-1192	AUCCCCAGUCACUAGGAGA	32
AD-46098.1	43	UCUUCACGGAAAAUCCGACA	1345-1363	UGUCGGAUUUUCCGUAAGA	44
AD-46111.1	63	UGAGACAGACCGCCAAAUA	1419-1437	UAUUUGGCGGUCUGUCUCA	64
AD-46103.1	29	UGGCACUUGGACUCUCCUA	1162-1180	UAGGAGAGUCCAAGUGCCA	30
AD-46120.1	19	UGGCGCUGCAACCGGUGUA	554-572	UACACCGGUUGCAGCGCCA	20
AD-46125.1	99	UGGUUAUGGGUCCUAUAAA	1578-1596	UUUAUAGGACCCAUAACCA	100
AD-46115.1	33	UGGUUUUCCACGAAUGGA	1251-1269	UCCAUUCGUGGGAAAACCA	34
AD-46134.1	55	UGUCCAAACUGUCGUGCAA	1394-1412	UUGCACGACAGUUUGGACA	56
AD-46101.1	91	UGUGGCUGAUUAUAACUGU	1556-1574	ACAGUUAUAUCAGCCACA	92
AD-46121.1	35	UUUCCCACGAAUGGACCCU	1255-1273	AGGGUCCAUUCGUGGGAAA	36
AD-46108.1	15	UUUUGGGUUCGGAGGAUCA	440-458	UGAUCCUCCGAACCCAAAA	16

TABLE 2A-3

Human KLF1 Modified siRNA Duplex Sequences					
Duplex ID	SEQ ID NO.: (sense)	Sense sequence	Position in NM_006563.3	Antisense Sequence	SEQ ID NO.: (antisense)
AD-46099.1	528	AAAcuGucGuGcAAAcccAdTsdT	1399-1417	UGGGUUUGcACGAcAGUUUdTsdt	529
AD-46132.1	530	AAGcGAGGccGAcGuucGudTsdt	856-874	ACGAACGUCGGCCUCGCUUdTsdt	531
AD-46094.1	532	AAuAAAcGGAcucAGuGGAdTsdt	1434-1452	UccACUGAGUCCGUUuAUUdTsdt	533

TABLE 2A-3 -continued

Human KLF1 Modified siRNA Duplex Sequences					
Duplex ID	SEQ ID NO.: (sense)	Sense sequence	Position in NM_006563.3	Antisense Sequence	SEQ ID NO.: (antisense)
AD-46113.1	534	AAuGGUuAuGGGUccuAuAdTsdT	1576-1594	uAuAGGACCCcAuAACcAUUdTsdt	535
AD-46123.1	536	AGAcAGAccGccAAuAAAdTsdt	1421-1439	UUuAUUUGGCGGUCUGUCUdTsdt	537
AD-46129.1	538	AGAccGccAAuAAcGGAdTsdt	1425-1443	UCCGUUuAUUUGGCGGUCUdTsdt	539
AD-46091.1	540	AGcucuGcccAcGuGcuuudTsdt	1088-1106	AAAGcACGUGGGcAGAGCUdTsdt	541
AD-46090.1	542	AGuGGuGGcGuccGAAGAdTsdt	149-167	UCUUCGGAGCGCcACcACUdTsdt	543
AD-46119.1	544	AuGGUuAuGGGUccuAuAdTsdt	1577-1595	UuAuAGGACCCcAuAACcAUdTsdt	545
AD-46128.1	546	AuGuccAAAcuGucGuGcAdTsdt	1393-1411	UGcACGAcAGUUUGGAcAUdTsdt	547
AD-46133.1	548	cAAAGAuccAcccAAuAudTsdt	1292-1310	AuAUUUGGGUGGAUCUUUGdTsdt	549
AD-46107.1	550	cAAuGGUuAuGGGUccuAudTsdt	1575-1593	AuAGGACCCcAuAACcAUUGdTsdt	551
AD-46136.1	552	cccuuAuGuGGcuGAuAudTsdt	1549-1567	AuAUcAGCcAcAAuAAGGGdTsdt	553
AD-46126.1	554	ccuccuuccuGAGUuGuuudTsdt	761-779	AAAcAACUcAGGAAGGAGGdTsdt	555
AD-46124.1	556	ccuGAAGGUccuuAuGudTsdt	1540-1558	AcAAuAAGGGACCUUcAGGdTsdt	557
AD-46095.1	558	ccuuAuGuGGcuGAuAuudTsdt	1550-1568	AAuAUcAGCcAcAAuAAGGdTsdt	559
AD-46095.3	560	ccuuAuGuGGcuGAuAuudTsdt	1550-1568	AAuAUcAGCcAcAAuAAGGdTsdt	561
AD-46102.1	562	cGAGAcucuGGGcGcAuAdTsdt	393-411	AuAUGCGCCcAGAGUCUCGdTsdt	563
AD-46135.1	564	cGccAAuAAcGGAcucAdTsdt	1429-1447	UGAGUCCGUUuAUUUGCGdTsdt	565
AD-46110.1	566	cGAAAAuccGAcAAGccudTsdt	1350-1368	AGGCUUGUCGGAUUUCCGdTsdt	567
AD-46118.1	568	cuccuGAAGGUccuuAuudTsdt	1538-1556	AAuAAGGGACCUUcAGGAGdTsdt	569
AD-46127.1	570	cuGGAcucGcGuucccAAAdTsdt	1277-1295	UUUGGGAACCGAGUCcAGdTsdt	571
AD-46106.1	572	cuGGGucuAGAAAGcGGcudTsdt	1521-1539	AGCCGCUUUCuAGACCcAGdTsdt	573
AD-46104.1	574	cuuAcGGAAAuccGAcAAAdTsdt	1346-1364	UUGUCGGAUUUCCGuAAGdTsdt	575
AD-46100.1	576	GAcucAGuGGAcAcucAGAdTsdt	1442-1460	UCUGAGUGUCcACUGAGUCdTsdt	577
AD-46117.1	578	GAGAcAGAccGccAAuAAAdTsdt	1420-1438	UuAUUUGGCGGUCUGUCUdTsdt	579
AD-46122.1	580	GAGAuGuccAAAcuGucGudTsdt	1390-1408	ACGAcAGUUUGGAcAUCUCdTsdt	581
AD-46096.1	582	GccccuccAcGuGAAGucudTsdt	210-228	AGACUUCcACGUGGAGGGCdTsdt	583
AD-46097.1	584	GccccGGcAcuuGGAcucudTsdt	1158-1176	AGAGUCcAAGUGCcAGGGCdTsdt	585
AD-46112.1	586	GcuccuGAAGGUccuuAudTsdt	1537-1555	AuAAGGGACCUUcAGGAGCdTsdt	587
AD-46116.1	588	GGAAAuccGAcAAGccudTsdt	1351-1369	AAGGCUUGUCGGAUUUCCdTsdt	589
AD-46093.1	590	GuccAAAcuGucGuGcAAAdTsdt	1395-1413	UUUGcACGAcAGUUUGGACdTsdt	591
AD-46105.1	592	GuGcAAAcccAGuGAGAcAdTsdt	1407-1425	UGUCUcACUGGGUUUGcACdTsdt	593
AD-46092.1	594	uAucAAAcAcGGAcccAuAdTsdt	1308-1326	uAUGGUCCGUGUUUGAuAdTsdt	595
AD-46130.1	596	ucccuuAuGuGGcuGAuAdTsdt	1548-1566	uAUcAGCcAcAAuAAGGGAdTsdt	597
AD-53284.1	598	UCCCUUAUUGUGGCUGAUUAU	1546-1568	AAUAUCAGCCACAAUAAGGGACC	599
AD-53290.1	560	UfcCfcUfuAfuUfgUfgGfcUfg AfuAfuUf	1546-1568	aAfuAfuCfaGfcCfaCfaAfuAf aGfgGfaCfc	561
AD-53295.1	562	UfcCfcUfuAfuUfgUfgGfcUfg AfuAfuUf	1546-1568	aAfuAfuCfaGfcCfaCfaAfuAf aGfgGfasCfsc	563
AD-53301.1	564	UfcCfcUfuAfuUfgUfgGfcUf gAfuAfuUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa GfgGfasCfs	565

TABLE 2A-3 -continued

Human KLF1 Modified siRNA Duplex Sequences					
Duplex ID	SEQ ID NO.: (sense)	Sense sequence	Position in NM_006563.3	Antisense Sequence	SEQ ID NO.: (antisense)
AD-53307.1	566	UfcCfcUfuauUfGfUfgGfcUf gAfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAf aGfgGfasCfsc	567
AD-53308.1	568	UfcCfcUfUfAfuUfGfUfgGfcU fgAfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAaG fgGfasCfsc	569
AD-53309.1	570	UfcCfcuuAfuUfGfUfgGfcUfg AfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfA fGfgGfasCfsc	571
AD-53310.1	572	UfcCfcUfuAfuUfGfUfgGfcU fgAfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa ggGfasCfsc	573
AD-53311.1	574	UfcUfuAfuUfGfUfgGfcUfg AfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa GfGfGfasCfsc	575
AD-53312.1	576	UfcCfcUfuAfuUfGfUfgGfcU fgAfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa GfggasCfsc	577
AD-53313.1	578	ucCfcUfuAfuUfGfUfgGfcUfg AfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa GfgGfAfsCfsc	579
AD-53314.1	580	UfcCfcUfuAfuUfGfUfgGfcUf gAfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAfa GfgGfascsc	581
AD-53315.1	582	UfcCfcUfuAfuUfGfUfggcUfg AfuAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAf aGfgGfasCfsc	583
AD-53316.1	584	UfcCfcUfuAfuUfGfUfgGfcUf fgAfuAfusUf	1546-1568	aAfuAfuCfagcCfacaAfuAfaG fgGfasCfsc	585
AD-53317.1	586	UfcCfcUfuAfuUfGfUfgGfcug AfuAfusUf	1546-1568	aAfuAfuCfAfGfcCfacaAfuAf aGfgGfasCfsc	587
AD-53318.1	588	UfcCfcUfuAfuUfGfUfgGfcUf GfAfuAfusUf	1546-1568	aAfuAfucaGfcCfacaAfuAfaG fgGfasCfsc	589
AD-53319.1	590	UfcCfcUfuAfuUfGfUfgGfcUf gauAfusUf	1546-1568	aAfuAfuCfaGfcCfacaAfuAf aGfgGfasCfsc	591
AD-53320.1	592	UfcCfcUfuAfuUfGfUfgGfcUf gAfUfAfusUf	1546-1568	aAfuauCfaGfcCfacaAfuAfaG fgGfasCfsc	593
AD-53321.1	594	UfcCfcUfuAfuUfGfUfgGfcUf gAfuausUf	1546-1568	aAfUfAfuCfaGfcCfacaAfuAf aGfgGfasCfsc	595
AD-53322.1	596	UfcCfcUfuAfuUfGfUfgGfcUf gAfuAfuUfUf	1546-1568	aaUfuCfaGfcCfacaAfuAfaG fgGfasCfsc	597
AD-46114.1	598	ucGGAGGAucAcucGGGuudTsdT	448-466	AACCCGAGUGAUCCUGCAdTsdT	599
AD-46109.1	600	ucuccuAGuGAcuGGGAudTsdT	1174-1192	AUCCCCAGUcAcuAGGAGAdTsdT	601
AD-46098.1	602	ucuuAcGGAAAuccGAcAdTsdT	1345-1363	UGUCGGAUUUCCGuAAGAdTsdT	603
AD-46111.1	604	uGAGACAGAccGccAAAUAdTsdT	1419-1437	uAUUUGGCGGUCUGUCUcAdTsdT	605
AD-46103.1	606	uGGcAcuuGGAucucuccuAdTsdT	1162-1180	uAGGAGAGUccAAGUGCcAdTsdT	607
AD-46120.1	608	uGGcGcuGcAAccGGuGuAdTsdT	554-572	uAcACCGGUUGcAGCGCcAdTsdT	609
AD-46125.1	610	uGGuuAuGGGuuccuAuAAAdTsdT	1578-1596	UUuAuAGGACCcAuAACcAdTsdT	611
AD-46115.1	612	uGGuuuuuccAcGAAuGGAdTsdT	1251-1269	UCCAUUCGUGGAAAACcAdTsdT	613
AD-46134.1	614	uGuccAAAcuGucGuGcAAAdTsdT	1394-1412	UUGcACGAcAGUUUGGAcAdTsdT	615
AD-46101.1	616	uGuGGcuGAuAuAAcuGudTsdT	1556-1574	AcAGUuAAuAUcAGCcAcAdTsdT	617
AD-46121.1	618	uuucccAcGAAuGGAccudTsdT	1255-1273	AGGGUCCcAUUCGUGGAAAAdTsdT	619
AD-46108.1	620	uuuuGGGuucGGAGGAucAdTsdT	440-458	UGAUCCUCCGAACCcAAAAdTsdT	621

TABLE 2B

Mouse KLf1 Single Strands and Duplex Sequences				
SEQ ID NO: (sense)	Position of 5' base on transcript (sense)	NM_010635.2 sense (5'-3')	antisense (5'-3')	SEQ ID NO: (antisense)
103	13	GAGCCCUCCAAGAAACUUU	AAAGUUUCUUGGAGGGCUC	104
105	24	GAAACUUUCCUAGCCUCAU	AUGAGGCUAGGAAAGUUUC	106
107	37	CCUCAUAGCCCAUGAGGCA	UGCCUCAUGGGCUAUGAGG	108
109	111	GCUGAGACUGUCUUACCCU	AGGGUAAGACAGUCUCAGC	110
111	114	GAGACUGUCUUACCCUCCA	UGGAGGGUAAGACAGUCUC	112
113	174	GAGGACUUCUCAAGUGGU	ACCACUUGAGGAAGUCCUC	114
115	197	GUCUGAGGAGACGCAGGAU	AUCCUGCGUCUCCUCAGAC	116
117	247	CGUCCCAUCACGUGAGUCU	AGACUCACGUGAUGGGACG	118
119	250	CCCAUCACGUGAGUCUGAA	UUCAGACUCACGUGAUGGG	120
121	251	CCAUCACGUGAGUCUGAAA	UUUCAGACUCACGUGAUGG	122
123	264	CUGAAAU CGGAGGACCCUU	AAGGGUCCUCCGAUUUCAG	124
125	294	GAUGAGAGGGACGUGACCU	AGGUCACGUCCUCUCAUC	126
127	315	GCGUGGGACCCGGAUCUUU	AAAGAUCGGGUCCACGC	128
129	316	CGUGGGACCCGGAUCUUU	AAAAGAUCGGGUCCACG	130
131	323	CCCGGAUCUUUCCUUACA	UGUAAGGAAAAGAUCCGGG	132
133	324	CCGGAUCUUUCCUUACAA	UUGUAAGGAAAAGAUCCGG	134
135	325	CGGAUCUUUCCUUACAAA	UUUGUAAGGAAAAGAUCCG	136
137	340	CAAACUUUCCAGGUUCCGA	UCGGAACCGGAAAGUUUG	138
139	344	CUUUCAGGUUCCGAGUCU	AGACUCGGAACCGGAAAG	140
141	403	GGCCAGUGGCACAGUUCGA	UCGAACUGUGCCACUGGCC	142
143	781	CUUCCUUCUUGAAUUGUCU	AGACAAUUAAGAAGGAAG	144
145	887	CAGCCGGCGAACUUUGGCA	UGCCAAAGUUCGCCGGCUG	146
147	892	GGCGAACUUUGGCACCUAA	UUAGGUGCCAAAGUUCGCC	148
149	894	CGAACUUUGGCACCUAAGA	UCUUAGGUGCCAAAGUUCG	150
151	1050	GCUCGCUCAGACGAACUGA	UCAGUUCGUCUGAGCGAGC	152
153	1082	GAAGCACACUGGACAUCGU	ACGAUGUCCAGUGUCUUC	154
155	1114	GCCUCUGCCCACGUGCUUU	AAAGCACGUGGGCAGAGGC	156
157	1141	CUGACCACUUAGCUCUGCA	UGCAGAGCUAAGUGGUCAG	158
159	1146	CACUUAGCUCUGCACAUGA	UCAUGUGCAGAGCUAAGUG	160
161	1190	CAAGGACUGGGGAUGAAAU	AUUUCAUCCCCAGUCCUUG	162
163	1196	CUGGGGAUGAAAUAAGAGU	ACUCUUAUUUCAUCCCCAG	164
165	1200	GGAUGAAAUAAGAGUGGAU	AUCCACUCUUAUUUCAUCC	166
167	1213	GUGGAUCCAAGGACCGUAU	AUACGGUCCUUGGAUCCAC	168
169	1219	CCAAGGACCGUAUCCAAA	UUUGGGAUACGGUCCUUGG	170
171	1233	CCAAAGAUGGGCCAUUAU	AUAAUGGCCCAUCUUUUGG	172
173	1242	GGGCCAUUAUAUAGUCCUA	UAGGACUAUAUAAUGGCC	174

TABLE 2B -continued

Mouse KLf1 Single Strands and Duplex Sequences				
SEQ ID NO:	Position of 5' base on transcript			SEQ ID NO:
(sense)	NM_010635.2 sense (5'-3')	antisense (5'-3')		(antisense)
175	1246	CAUUUAUAGUCCUACCCA	UGGGUAGGACUAUAUAUG	176
177	1279	CAGAAGACCAUACAAAGGA	UCCUUUGUAUGGUCUUCUG	178
179	1296	GAGCCUUCAGGACAAACCU	AGGUUUGUCCUGAAGGCUC	180
181	1303	CAGGACAAACCUACAUGU	ACAUGUGAGGUUUGUCCUG	182
183	1351	GACCCAGCAAUAUAGACCA	UGGUCUAUAUUGCUGGGUC	184
185	1368	CACCAGAUAAAUCAACUCA	UGAGUUGAUUUUUCUGGUG	186
187	1431	GAUGGACUGGGUGAGAUU	AAUCUCACCCAGUCCAUC	188
189	1482	CCCAUCUGCUAGGAUUGUU	AACAAUCCUAGCAGAUGGG	190
191	1487	CUGCUAGGAUUGUUGUCGU	ACGACAACAAUCCUAGCAG	192
193	1493	GGAUUGUUGUCGUUACUAV	AUAGUAACGACAACAAUCC	194
195	1494	GAUUGUUGUCGUUACUAVA	UAUAGUAACGACAACAAUC	196

TABLE 2C

BCL11A Single Strands and Duplex Sequences to match transcript variants 1, 2 and 3 of human and mouse BCL11A (human sequence references NM_022893.3 (variant 1), NM_018014.3 (variant 2), and NM_138559.1 (variant 3))					
Table 2C includes unmodified siRNAs targeting all BCL11a isoforms.					
Duplex Name	SEQ ID NO.: Sense Sequence	Position relative to NM_022893.3 SEQ ID NO: 3	Start	SEQ ID NO.: Antisense Sequence	
	197 UUCUUAUUUUUAUCGAGCA	407-425	407	198 UGCUCGAUAAAAUAAGAA	
	229 UUGUUUAUACAACGUCAUCU	561-579	561	230 AGAUGACGUUGAUAAACAA	
	291 AUUAAGAAUCUACUUGAA	810-828	810	292 UUCUAAGUAGAUUCUUAU	
AD-46498.1	213 CCAGAGGAUGACGAUUGUU	547-565	547	214 AACAAUCGUCAUCCUCUGG	
AD-46500.1	245 AGGAACACAUAGCAGAUAA	599-617	599	246 UUAUCUGCUAUGUGUUCU	
AD-46501.1	261 GCCCAGCAGCUACACAUGU	726-744	726	262 ACAUGUGUAGCUGCUGGGC	
AD-46502.1	277 CACAGAACACUCAUGGAUU	794-812	794	278 AAUCCAUGAGUGUUCUGUG	
AD-46503.1	199 UAUUUUUUAUCGAGCACAAA	411-429	411	200 UUUGUGCUCGAUAAAAUA	
AD-46504.1	215 CAGAGGAUGACGAUUGUUU	548-566	548	216 AAACAAUCGUCAUCCUCUG	
AD-46505.1	231 UGUUUUAUACAACGUCAUCUA	562-580	562	232 UAGAUGACGUUGAUAAACA	
AD-46506.1	247 GGAACACAUAGCAGAUAAA	600-618	600	248 UUUUUCUGCUAUGUGUUC	
AD-46507.1	263 CCCAGCAGCUACACAUGUA	727-745	727	264 UACAUGUGUAGCUGCUGGG	
AD-46508.1	279 CAGAACACUCAUGGAUUA	796-814	796	280 UUAUCCAUAGAGUGUUCUG	
AD-46509.1	201 UUUUUCGAGCACAACGGGA	415-433	415	202 UCCGUUUGUGCUCGAUAAA	
AD-46510.1	217 AGAGGAUGACGAUUGUUUA	549-567	549	218 UAAACAAUCGUCAUCCUCU	
AD-46511.1	233 UUUUAUACAACGUCAUCUAGA	564-582	564	234 UCUAGAUGACGUUGAUAAA	
AD-46512.1	249 ACAUAGCAGAUAAACUUCU	605-623	605	250 AGAAGUUUAUCUGCUAUGU	
AD-46513.1	265 AGCUACACAUGUACAACUU	733-751	733	266 AAGUUGUACAUGUGUAGCU	

TABLE 2C -continued

BCL11A Single Strands and Duplex Sequences to match transcript variants 1, 2 and 3 of human and mouse BCL11A (human sequence references NM_022893.3 (variant 1), NM_018014.3 (variant 2), and NM_138559.1 (variant 3)) Table 2C includes unmodified siRNAs targeting all BCL11a isoforms.						
Duplex Name	SEQ ID NO.: Sense Sequence	Position relative to NM_022893.3 SEQ ID NO: 3 Start	SEQ ID NO.: Antisense Sequence			
AD-46514.1	281 GAACACUCAUGGAUUAAGA	798-816	798	282	UCUUAUCCAUGAGUGUUC	
AD-46515.1	203 AUGGCAGCCUCUGCUUAGA	443-461	443	204	UCUAAGCAGAGGCUGCCA	
AD-46516.1	219 GAGGAUGACGAUUGUUUAU	550-568	550	220	AUAAACAAUCGUCAUCCUC	
AD-46517.1	235 AUC AACGUCAUCUAGAGGA	567-585	567	236	UCCUCUAGAUGACGUUGAU	
AD-46518.1	251 UGCCCCGCAGGGUAUUUGU	699-717	699	252	ACAAAUACCCUGCGGGGCA	
AD-46519.1	267 UACACAUGUACAACUUGCA	736-754	736	268	UGCAAGUUGUACAUGUGUA	
AD-46520.1	283 AACACUCAUGGAUUAAGAA	799-817	799	284	UUCUUAUCCAUGAGUGUU	
AD-46521.1	205 GCAGCCUCUGCUUAGAAAA	446-464	446	206	UUUUCUAAGCAGAGGCUCG	
AD-46522.1	221 GGAUGACGAUUGUUUAUCA	552-570	552	222	UGAUAAACAAUCGUCAUCC	
AD-46523.1	237 UCAACGUCAUCUAGAGGAA	568-586	568	238	UUCCUCUAGAUGACGUUGA	
AD-46524.1	253 GCCCCGCAGGGUAUUUGUA	700-718	700	254	UACAAAUACCCUGCGGGGC	
AD-46525.1	269 ACACAUGUACAACUUGCAA	737-755	737	270	UUGCAAGUUGUACAUGUGU	
AD-46526.1	285 ACACUCAUGGAUUAAGAAU	800-818	800	286	AUUCUUAUCCAUGAGUGU	
AD-46527.1	207 CAGCCUCUGCUUAGAAAAA	447-465	447	208	UUUUUCUAAGCAGAGGCUG	
AD-46528.1	223 GACGAUUGUUUAUCAACGU	556-574	556	224	ACGUUGAUAAACAAUCGUC	
AD-46529.1	239 ACGUCAUCUAGAGGAUUU	571-589	571	240	AAAUUCCUCUAGAUGACGU	
AD-46530.1	255 CCCCGCAGGGUAUUUGUAA	701-719	701	256	UUACAAAUACCCUGCGGGG	
AD-46531.1	271 UACAACUUGCAAACAGCCA	744-762	744	272	UGGCUGUUUGCAAGUUGUA	
AD-46532.1	287 ACUCAUGGAUUAAGAAUCU	802-820	802	288	AGAUUCUUAUCCAUGAGU	
AD-46533.1	209 ACGCCAGAGGAUGACGAUU	544-562	544	210	AAUCGUCAUCCUCUGGCGU	
AD-46534.1	225 CGAUUGUUUAUCAACGUCA	558-576	558	226	UGACGUUGAUAAACAAUCG	
AD-46535.1	241 CAAACAGGAACACAUGCA	594-612	594	242	UGCUAUGUGUUCUGUUUG	
AD-46536.1	257 CCCGCAGGGUAUUUGUAAA	702-720	702	258	UUUACAAAUACCCUGCGGG	
AD-46537.1	273 AACACGCACAGAACACUCA	788-806	788	274	UGAGUGUUCUGGCGUGUU	
AD-46538.1	289 GAUUAAGAAUCUACUUAGA	809-827	809	290	UCUAAGUAGAUUCUUAUUC	
AD-46539.1	211 GCCAGAGGAUGACGAUUGU	546-564	546	212	ACAAUCGUCAUCCUCUGGC	
AD-46540.1	227 GAUUGUUUAUCAACGUCAU	559-577	559	228	AUGACGUUGAUAAACAAUC	
AD-46541.1	243 CAGGAACACAUAGCAGAU	598-616	598	244	UAUCUGCUAUGUGUCCUG	
AD-46542.1	259 CGCAGGGUAUUUGUAAAGA	704-722	704	260	UCUUUACAAAUACCCUGCG	
AD-46543.1	275 GCACAGAACACUCAUGGAU	793-811	793	276	AUCCAUGAGUGUUCUGUC	

TABLE 3

Modified siRNAs targeting all BCL11a isoforms.							
Duplex Name	SEQ ID NO.: Sense	OligoSeq	Position relative to NM_022893.3 SEQ ID NO.: 3	Start	SEQ ID NO.: Antisense	OligoSeq	
AD-46498.1	305	ccAGAGGAuGAcGAuuGuudTsdT	547-565	547	306	AAcAAUCGUcAUCCUCUGGdTsdT	
AD-46500.1	335	AGGAACAcAuAGcAGAuAAAdTsdT	599-617	599	336	UuAUCUGCuAUGUGUUCcUdTsdT	
AD-46501.1	351	GcccAGcAGcuAcAcAuGudTsdT	726-744	726	352	AcAUGUGuAGCUGCUGGGCdTsdT	
AD-46502.1	367	cAcAGAAcAcucAuGGAuudTsdT	794-812	794	368	AAUCcAUGAGUGUUCUGUGdTsdT	
AD-46503.1	291	uAuuuuuAucGAGcAcAAAdTsdT	411-429	411	292	UUUGUCUCGAuAAAAAuAdTsdT	
AD-46504.1	307	cAGAGGAuGAcGAuuGuudTsdT	548-566	548	308	AAAcAAUCGUcAUCCUCUGdTsdT	
AD-46505.1	321	uGuuuAucAAcGucAucuAdTsdT	562-580	562	322	uAGAUGACGUUGAuAAAcAdTsdT	
AD-46506.1	337	GGAACAcAuAGcAGAuAAAdTsdT	600-618	600	338	UUuAUCUGCuAUGUGUUCcUdTsdT	
AD-46507.1	353	cccAGcAGcuAcAcAuGuAdTsdT	727-745	727	354	uAcAUGUGuAGCUGCUGGGdTsdT	
AD-46508.1	369	cAGAAcAcucAuGGAuuAAAdTsdT	796-814	796	370	UuAAUCcAUGAGUGUUCUGdTsdT	
AD-46509.1	293	uuuAucGAGcAcAAAcGGAdTsdT	415-433	415	294	UCCGUUUGUGCUCGAuAAAdTsdT	
AD-46510.1	309	AGAGGAuGAcGAuuGuuuAdTsdT	549-567	549	310	uAAAcAAUCGUcAUCCUCUdTsdT	
AD-46511.1	323	uuuAucAAcGucAucuAGAdTsdT	564-582	564	324	UCuAGAUGACGUUGAuAAAdTsdT	
AD-46512.1	339	AcAuAGcAGAuAAAcuucUdTsdT	605-623	605	340	AGAAGUUuAUCUGCuAUGUdTsdT	
AD-46513.1	355	AGcuAcAcAuGuAcAAcuUdTsdT	733-751	733	356	AAGUUGuAcAUGUGuAGCUdTsdT	
AD-46514.1	371	GAAcAcucAuGGAuuAAGAdTsdT	798-816	798	372	UCUuAAUCcAUGAGUGUUCdTsdT	
AD-46515.1	295	AuGGcAGccucUcGuuAGAdTsdT	443-461	443	296	UCuAAGcAGAGGCUGCcAUdTsdT	
AD-46516.1	311	GAGGAuGAcGAuuGuuuAdTsdT	550-568	550	312	AuAAAcAAUCGUcAUCCUCdTsdT	
AD-46517.1	325	AucAAcGucAucuAGAGGAdTsdT	567-585	567	326	UCCUCuAGAUGACGUUGAUdTsdT	
AD-46518.1	341	uGccccGcAGGGuAuuuGuAdTsdT	699-717	699	342	AcAAAuACCCUGCGGGcAdTsdT	
AD-46519.1	357	uAcAcAuGuAcAAcuUcAdTsdT	736-754	736	358	UGcAAGUUGuAcAUGUGuAdTsdT	
AD-46520.1	373	AAcAcucAuGGAuuAAGAAAdTsdT	799-817	799	374	UUCUuAAUCcAUGAGUGUUDdTsdT	
AD-46521.1	297	GcAGccucUcGuuAGAAAAdTsdT	446-464	446	298	UUUUCuAAGcAGAGGCUGCdTsdT	
AD-46522.1	313	GGAuGAcGAuuGuuuAucAdTsdT	552-570	552	314	UGAuAAAcAAUCGUcAUCCdTsdT	
AD-46523.1	327	ucAAcGucAucuAGAGGAAdTsdT	568-586	568	328	UUCCUCuAGAUGACGUUGAdTsdT	
AD-46524.1	343	GccccGcAGGGuAuuuGuAdTsdT	700-718	700	344	uAcAAAuACCCUGCGGGCdTsdT	
AD-46525.1	359	AcAcAuGuAcAAcuUcAdTsdT	737-755	737	360	UUGcAAGUUGuAcAUGUGUdTsdT	
AD-46526.1	375	AcAcucAuGGAuuAAGAAuAdTsdT	800-818	800	376	AUUCUuAAUCcAUGAGUGUdTsdT	
AD-46527.1	299	cAGccucUcGuuAGAAAAAdTsdT	447-465	447	300	UUUUUCuAAGcAGAGGCUGdTsdT	
AD-46528.1	315	GAcGAuuGuuuAucAAcGudTsdT	556-574	556	316	ACGUUGAuAAAcAAUCGUCdTsdT	
AD-46529.1	329	AcGucAucuAGAGGAuuuAdTsdT	571-589	571	330	AAAUCCUCuAGAUGACGUdTsdT	
AD-46530.1	345	ccccGcAGGGuAuuuGuAdTsdT	701-719	701	346	UuAcAAAuACCCUGCGGGdTsdT	
AD-46531.1	361	uAcAAcuUcGcAAAcAGccAdTsdT	744-762	744	362	UGGCUGUUUGcAAGUUGuAdTsdT	
AD-46532.1	377	AcucAuGGAuuAAGAAucUdTsdT	802-820	802	378	AGAUCUuAAUCcAUGAGUdTsdT	
AD-46533.1	301	AcGccAGAGGAuGAcGAuudTsdT	544-562	544	302	AAUCGUcAUCCUCUGGCUdTsdT	
AD-46534.1	317	cGAuuGuuuAucAAcGucAdTsdT	558-576	558	318	UGACGUUGAuAAAcAAUCGdTsdT	

TABLE 3 -continued

Modified siRNAs targeting all BCL11a isoforms.						
Duplex Name	SEQ ID NO.: Sense	OligoSeq	Position relative to NM_022893.3 SEQ ID NO: 3	Start	SEQ ID NO.: Antisense	OligoSeq
AD-46535.1	331	cAAAcAGGAACAcAuAGcAdTsdT	594-612	594	332	UGCuAUGUGUCCUGUUUGdTsdT
AD-46536.1	347	cccGcAGGGuAuuuGuAAAdTsdT	702-720	702	348	UUuAcAAuAACCUGCGGdTsdT
AD-46537.1	363	AAcAcGcAcAGAAcAcucAdTsdT	788-806	788	364	UGAGUGUUCUGUGCGUUdTsdT
AD-46538.1	379	GAuuAAGAucuuAcuuAGAdTsdT	809-827	809	380	UCuAAGuAGAUUCUuAAUCdTsdT
AD-46539.1	303	GccAGAGGAuGAcGAuuGudTsdT	546-564	546	304	AcAAUCGUcAUCCUGGcTdTsdT
AD-46540.1	319	GAuuGuuuAucAAcGucAudTsdT	559-577	559	320	AUGACGUUGAuAAAaAAUCdTsdT
AD-46541.1	333	cAGGAACAcAuAGcAGAuAdTsdT	598-616	598	334	uAUCUGCuAUGUGUCCUGdTsdT
AD-46542.1	349	cGcAGGGuAuuuGuAAAGAdTsdT	704-722	704	350	UCUUuAcAAuAACCUGCGdTsdT
AD-46543.1	365	GcAcAGAAcAcucAuGGAdTsdT	793-811	793	366	AUCcAUGAGUGUUCUGUGCdTsdT

TABLE 4

Unmodified siRNAs specifically targeting BCL11a with the long form of exon 4.						
Duplex Name	SEQ ID NO.: Sense	Sequence	Position relative to NM_018014.3 SEQ ID NO: 4	sStart	SEQ ID NO.: Antisense	Sequence
AD-52060.1	81	UGGUAUCCCUUCAGGACUA	861-879	861	382	UAGUCCUGAAGGGAUACCA
AD-52061.1	97	AUACCAGGAUCAGUAUCGA	955-973	955	398	UCGAUACUGAUCCUGGUU
AD-52062.1	13	CCAGCCCUAUGCAAAGGUU	1235-1253	1235	414	AACCUUUGCAUAGGCGUGG
AD-52063.1	29	GUCGGACCGCAUAGACGAU	2007-2025	2007	430	AUCGUCUAUGCGGUCCGAC
AD-52064.1	45	AGGGAGCACGCCCCAUUU	2385-2403	2385	446	AAUAUGGGGCGUGUCCCU
AD-52065.1	83	CUAGGUGCAGAAUGUCCUU	877-895	877	384	AAGGACAUUCUGCACCUAG
AD-52066.1	99	ACCAGGAUCAGUAUCGAGA	957-975	957	400	UCUCGAUACUGAUCCUGGU
AD-52067.1	15	AAAGGUUACUGCAACCAUU	1247-1265	1247	416	AAUGGUUGCAGUAACCUUU
AD-52068.1	31	CGCUGAGCCCCUUCUCUAA	2111-2129	2111	432	UUAGAGAAGGGGCUACGCG
AD-52069.1	47	GGGAGCACGCCCCAUUUUA	2386-2404	2386	448	UAAUAUGGGGCGUGUCCC
AD-52070.1	85	GCCACCUCUCCAUGGGAUU	900-918	900	386	AAUCCCAUGGAGAGGUGGC
AD-52071.1	01	CACCACCGAGACAUACAUU	1031-1049	1031	402	AAGUGAUGUCUCGGUGGUG
AD-52072.1	17	AGUCCAAGUCAUGCGAGUU	1352-1370	1352	418	AACUCGCAUGACUUGGACU
AD-52073.1	33	GCCCCUUCUCUAAGCGCAU	2117-2135	2117	434	AUGCGCUUAGAGAAGGGGC
AD-52074.1	49	GAGCACGCCCCAUUUAGU	2388-2406	2388	450	ACUAAUAUGGGGCGUGCUC
AD-52075.1	87	UGCAGACAAUAACCCUUUU	924-942	924	388	AAAGGGGUUAUUGUCUGCA
AD-52076.1	03	CAGGGUGCUGCGGUUGAAU	1122-1140	1122	404	AUUCACCGCAGCACCCUG
AD-52077.1	19	CGCCACCACGAGAACAGCU	1795-1813	1795	420	AGCUGUUCUCUGGUGGCG
AD-52078.1	35	CUCCAGGCAGCUCAAAGAU	2223-2241	2223	436	AUCUUUGAGCUGCCUGGAG
AD-52079.1	51	CACGCCCCAUUUAGUGGU	2391-2409	2391	452	ACCACUAAUAUGGGGCGUG
AD-52080.1	89	ACAAUAACCCCUUUAACCU	929-947	929	390	AGGUUAAAGGGGUUAUUGU

TABLE 4 -continued

Unmodified siRNAs specifically targeting BCL11a with the long form of exon 4.							
Duplex Name	SEQ ID NO.:	Sense Sequence	Position relative to NM_018014.3 SEQ ID NO: 4	sStart	SEQ ID NO.:	Antisense Sequence	
AD-52081.1	05	CGGUUGAAUCCAUGGCUA	1132-1150	1132	406	UAGCCAUUGGAUUCACCG	
AD-52082.1	21	GUCCUGGCGGAGAAGCAUA	1921-1939	1921	422	UAUGCUUCUCGCCCAGGAC	
AD-52083.1	37	AGGCAGCUCAAAGAUGCCU	2227-2245	2227	438	AGGGAUCUUUGAGCUGCCU	
AD-52084.1	91	CCCCUUUAACCUUGCUAAGA	936-954	936	392	UCUUAGCAGGUUAAAGGGG	
AD-52085.1	07	GAGCCUCCCGCCAUGGAUU	1153-1171	1153	408	AAUCCAUGGCGGGAGGCUC	
AD-52086.1	23	UCCUGGGCGAGAAGCAUAA	1922-1940	1922	424	UUAUGCUUCUCGCCCAGGA	
AD-52087.1	39	GGCAGCUCAAAGAUGCCU	2228-2246	2228	440	AAGGGAUCUUUGAGCUGCC	
AD-52088.1	93	CCUUUAACCUUGCUAAGAAU	938-956	938	394	AUUCUUAGCAGGUUAAAGG	
AD-52089.1	09	AGCCUCCCGCCAUGGAUUU	1154-1172	1154	410	AAAUCCAUGGCGGGAGGCU	
AD-52090.1	25	GACACUUGCGACGAAGACU	1975-1993	1975	426	AGUCUUCGUCGCAAGUGUC	
AD-52091.1	41	CUCAAGAUCUUUCCUUA	2233-2251	2233	442	UAAGGAAGGGAUCUUUGAG	
AD-52092.1	95	AGAAUACCAGGAUCAGUUAU	952-970	952	396	AUACUGAUCCUGGUUAUUCU	
AD-52093.1	11	GGAUUUCUCUAGGAGACUU	1167-1185	1167	412	AAGUCUCCUAGAGAAUCC	
AD-52094.1	27	AGUCGGACCGCAUAGACGA	2006-2024	2006	428	UCGUCUAUGCGGUCCGACU	
AD-52095.1	43	ACUCCAGACAAUCGCCUUU	2261-2279	2261	444	AAAGGCGAUUGUCUGGAGU	

TABLE 5

Modified siRNAs specifically targeting BCL11a with the long form of exon 4.							
Duplex Name	SEQ ID NO.:	Sense OligoSeq	Position relative to NM_018014.3 SEQ ID NO:4	Start	SEQ ID NO.:	Antisense OligoSeq	
AD-52060.1	453	uGGuAuucccuucAGGAcuAdTsdT	861-879	861	454	uAGUCCUGAAGGGAuAcAdTsdT	
AD-52061.1	469	AuAccAGGAucAGuAucGAdTsdT	955-973	955	470	UCGAuACUGAUCCUGGuAuTsdT	
AD-52062.1	485	ccAGcccuAuGcAAAGGuudTsdT	1235-1253	1235	486	AACCUUUGcAuAGGGCUGGdTsdT	
AD-52063.1	501	GucGGAccGcAuAGAcGAdTsdT	2007-2025	2007	502	AUCGUCuAUGCGGUCCGACdTsdT	
AD-52064.1	517	AGGGAGcAcGccccAuAuudTsdT	2385-2403	2385	518	AAuAUGGGGCGUGCUCCCUdTsdT	
AD-52065.1	455	cuAGGuGcAGAAuGuccuudTsdT	877-895	877	456	AAGGAcAUUCUGcACCuAGdTsdT	
AD-52066.1	471	AccAGGAucAGuAucGAGAdTsdT	957-975	957	472	UCUCGAuACUGAUCCUGGUdTsdT	
AD-52067.1	487	AAAGGuuAcuGcAAccAuudTsdT	1247-1265	1247	488	AAUGGUUGcAGuAACCuuudTsdT	
AD-52068.1	503	cGcuGAGcccccucucuAAAdTsdT	2111-2129	2111	504	UuAGAGAAGGGGCUcAGCGdTsdT	
AD-52069.1	519	GGGAGcAcGccccAuAuAdTsdT	2386-2404	2386	520	uAAuAUGGGGCGUGCUCCCdTsdT	
AD-52070.1	457	GccAccucuccAuGGGAudTsdT	900-918	900	458	AAUCCcAUGGAGAGGUGGCdTsdT	
AD-52071.1	473	cAccAccGAGAcAucAcuudTsdT	1031-1049	1031	474	AAGUGAUGUCUCGGUGGUGdTsdT	
AD-52072.1	489	AGuccAAGucAuGcGAGuudTsdT	1352-1370	1352	490	AACUCGcAUGACUUGGACUdTsdT	
AD-52073.1	505	GcccccucucuAAGcGcAudTsdT	2117-2135	2117	506	AUGCGCUuAGAGAAGGGGCdTsdT	
AD-52074.1	521	GAGcAcGccccAuAuAGudTsdT	2388-2406	2388	522	ACuAAuAUGGGGCGUGCUCdTsdT	
AD-52075.1	459	uGcAGAcAAuAAcccccuuudTsdT	924-942	924	460	AAAGGGGUuAUUGUCUGcAdTsdT	

TABLE 5 -continued

Modified siRNAs specifically targeting BCL11a with the long form of exon 4.							
Duplex Name	SEQ ID NO.:	Sense OligoSeq	Position relative to NM_018014.3		SEQ ID NO.:	Antisense OligoSeq	Start
			SEQ ID NO.:	Start			
AD-52076.1	475	cAGGGGuGcuGcGGuuGAAudTsdT	1122-1140	1122	476	AUUCaAACCgAGcACCCUGdTsdT	
AD-52077.1	491	cGccAccAcGAGAAcAGcudTsdT	1795-1813	1795	492	AGCUGUUCUCGUGGUGCGdTsdT	
AD-52078.1	507	cuccAGGcAGcucAAAGAudTsdT	2223-2241	2223	508	AUCUUUGAGCUGCCUGGAGdTsdT	
AD-52079.1	523	cAcGccccAuAuuAGuGGudTsdT	2391-2409	2391	524	ACcACuAAuAUGGGGCGUGdTsdT	
AD-52080.1	461	AcAAuAAccccuuuAAccudTsdT	929-947	929	462	AGGUuAAAGGGGUuAUUGUdTsdT	
AD-52081.1	477	cGGuuGAAuccAAuGGcuAdTsdT	1132-1150	1132	478	uAGCcAUUGGAUUCaAACCgdTsdT	
AD-52082.1	493	GuccuGGGcGAGAAGcAuAdTsdT	1921-1939	1921	494	uAUGCUUCUCGCCcAGGACdTsdT	
AD-52083.1	509	AGGcAGcucAAAGAuccudTsdT	2227-2245	2227	510	AGGGAUCUUUGAGCUGCCUdTsdT	
AD-52084.1	463	ccccuuuAAccuGcuAAGAdTsdT	936-954	936	464	UCUuAGcAGGUuAAAGGGdTsdT	
AD-52085.1	479	GAGccucccGccAuGGAuudTsdT	1153-1171	1153	480	AAUCcAUGGCGGGAGGCUCdTsdT	
AD-52086.1	495	uccuGGGcGAGAAGcAuAdTsdT	1922-1940	1922	496	UuAUGCUUCUCGCCcAGGAdTsdT	
AD-52087.1	511	GGcAGcucAAAGAucccuudTsdT	2228-2246	2228	512	AAGGGAUCUUUGAGCUGCCdTsdT	
AD-52088.1	465	ccuuuAAccuGcuAAGAAudTsdT	938-956	938	466	AUUCUuAGcAGGUuAAAGGdTsdT	
AD-52089.1	481	AGccucccGccAuGGAuuudTsdT	1154-1172	1154	482	AAAUcAUGGCGGGAGGCUCdTsdT	
AD-52090.1	497	GAcAcuuGcGAGcGAAGAcudTsdT	1975-1993	1975	498	AGUCUUCGUCGcAAGUGUCdTsdT	
AD-52091.1	513	cucAAAGAucccuuccuuAdTsdT	2233-2251	2233	514	uAAGGAAGGGAUCUUUGAGdTsdT	
AD-52092.1	467	AGAAuAccAGGAucAGuAdTsdT	952-970	952	468	AuACUGAUCCUGGuAUUCUdTsdT	
AD-52093.1	483	GGAuucucuAGGAGAcuudTsdT	1167-1185	1167	484	AAGUCUCCuAGAGAAUCCdTsdT	
AD-52094.1	499	AGucGGAccGcAuAGAcGAdTsdT	2006-2024	2006	500	UCGUCuAUGCGGUCCGACUdTsdT	
AD-52095.1	515	AcuccAGAcAAucGccuuudTsdT	2261-2279	2261	516	AAAGGCGAUUGUCUGGAGUdTsdT	

TABLE 6

Unmodified siRNAs targeting BCL11a.				
Duplex Name	SEQ ID NO.:	(unmodified sense oligo Unmodified sense sequence)	SEQ ID NO.:	(unmodified anti-sense oligo Unmodified Anti-sense oligo sequence)
AD-46509.6	666	UUUAUCGAGCACAAACGGA	667	UCCGUUUGUGCUCGAUAAA
AD-53263.1	668	UUUUUAUCGAGCACAAACGGA	669	UCCGUUUGUGCUCGAUAAAAUA
AD-53264.1	670	UUUUUAUCGAGCACAAACGGA	671	UCCGUUUGUGCUCGAUAAAAUA
AD-53268.1	672	UUUUUAUCGAGCACAAACGGA	673	UCCGUUUGUGCUCGAUAAAAUA
AD-53269.1	674	UUUUUAUCGAGCACAAACGGA	675	UCCGUUUGUGCUCGAUAAAAUA
AD-53270.1	676	UUUUUAUCGAGCACAAACGGA	678	UCCGUUUGUGCUCGAUAAAAUA
AD-53275.1	679	UUUUUAUCGAGCACAAACGGA	680	UCCGUUUGUGCUCGAUAAAAUA
AD-53276.1	681	UUUUUAUCGAGCACAAACGGA	682	UCCGUUUGUGCUCGAUAAAAUA
AD-53279.1	683	UUUUUAUCGAGCACAAACGGA	684	UCCGUUUGUGCUCGAUAAAAUA
AD-53280.1	685	UUUUUAUCGAGCACAAACGGA	686	UCCGUUUGUGCUCGAUAAAAUA

TABLE 6 -continued

Unmodified siRNAs targeting BCL11a.				
Duplex Name	SEQ ID NO.: (unmodified sense oligo sequence)	Unmodified Sense Sequence	SEQ ID NO.: (unmodified anti-sense oligo sequence)	Unmodified Anti-sense oligo Sequence
AD-53281.1	687	UUUUUAUCGAGCACAAACGGA	688	UCCGUUUGUGCUCGAUAAAAAUA
AD-53285.1	689	UUUUUAUCGAGCACAAACGGA	690	UCCGUUUGUGCUCGAUAAAAAUA
AD-53286.1	691	UUUUUAUCGAGCACAAACGGA	692	UCCGUUUGUGCUCGAUAAAAAUA
AD-53287.1	693	UUUUUAUCGAGCACAAACGGA	694	UCCGUUUGUGCUCGAUAAAAAUA
AD-53291.1	695	UUUUUAUCGAGCACAAACGGA	696	UCCGUUUGUGCUCGAUAAAAAUA
AD-53292.1	697	UUUUUAUCGAGCACAAACGGA	698	UCCGUUUGUGCUCGAUAAAAAUA
AD-53296.1	699	UUUUUAUCGAGCACAAACGGA	700	UCCGUUUGUGCUCGAUAAAAAUA
AD-53297.1	701	UUUUUAUCGAGCACAAACGGA	702	UCCGUUUGUGCUCGAUAAAAAUA
AD-53302.1	703	UUUUUAUCGAGCACAAACGGA	704	UCCGUUUGUGCUCGAUAAAAAUA
AD-53303.1	705	UUUUUAUCGAGCACAAACGGA	706	UCCGUUUGUGCUCGAUAAAAAUA

TABLE 7

Modified siRNAs targeting BCL11a.					
Duplex Name	SEQ ID NO.: (Modified Sense Oligo)	Modified Sense Oligo Sequence	SEQ ID NO.: (Modified Anti-sense Oligo)	Modified Antisense Oligo Sequence	
AD-46509.6	626	uuuAucGAGcAcAAcGGAdTsdT	627	UCCGUUUGUGCUCGAuAAAdTsdT	
AD-53263.1	628	uuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	629	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53264.1	630	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	631	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasusa	
AD-53268.1	632	UUUUUAUCGAGCACAAACGGA	633	UCCGUUUGUGCUCGAUAAAAAUA	
AD-53269.1	634	UfuUfuUfaUfcGfAfGfcacAfaAfcGfgsAf	635	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53270.1	636	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	637	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53275.1	638	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	639	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53276.1	640	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	641	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53279.1	642	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	643	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53280.1	644	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	645	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53281.1	646	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	647	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53285.1	648	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	649	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53286.1	650	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	651	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53287.1	652	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	653	uccGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53291.1	654	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	655	uCfcGfuUfuGfuGfcucGfAfUfaAfaAfasUfsa	
AD-53292.1	656	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	657	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53296.1	658	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	659	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53297.1	660	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	661	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53302.1	662	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	663	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	
AD-53303.1	664	UfuUfuUfaUfcGfAfGfcAfcAfaAfcGfgsAf	665	uCfcGfuUfuGfuGfcucGfaUfaAfaAfasUfsa	

### In vitro Screening of BCL11a siRNA Duplexes for BCL11a Knockdown Activity

BCL11a siRNA duplexes were screened for the ability to knockdown BCL11a expression in vitro. Knockdown of both endogenous and exogenously expressed BCL11a were evaluated.

In vitro Screening:

Cell Culture and Transfections:

H441, WI-38, or Hep3B cells (ATCC, Manassas, Va.) were grown to near confluence at 37° C. in an atmosphere of 5% CO<sub>2</sub> in RPMI (for H441), EMEM (for WI-38 and Hep3B) (ATCC) supplemented with 10% FBS, streptomycin, and glutamine (ATCC) before being released from the plate by trypsinization. Transfection was carried out by adding 14.8 ul of Opti-MEM plus 0.2 ul of Lipofectamine RNAiMax per well (Invitrogen, Carlsbad Calif. cat #13778-150) to 5 ul of siRNA duplexes per well into a 96-well plate and incubated at room temperature for 15 minutes. 80 ul of complete growth media without antibiotic containing ~2×10<sup>4</sup> HeLa or Hep3B cells were then added to the siRNA mixture. Cells were incubated for either 24 or 120 hours prior to RNA purification. For knockdown of endogenously expressed BCL11a, single dose experiments were performed at 10 nM and 0.1 nM final duplex concentration and dose response experiments were done at 10, 1, 0.5, 0.1, 0.05, 0.01, 0.005, 0.001, 0.0005, 0.0001, 0.00005, 0.00001 nM final duplex concentration. For screens in which BCL11a was expressed from a plasmid the final siRNA concentration was 50 nM.

Total RNA Isolation Using DYNABEADS mRNA Isolation Kit (Invitrogen, Part #: 610-12):

Cells were harvested and lysed in 150 ul of Lysis/Binding Buffer then mixed for 5 minute at 850 rpm using an Eppendorf Thermomixer (the mixing speed was the same through-

cDNA Synthesis Using ABI High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, Calif., Cat #4368813):

A master mix of 2 ul of 10× Buffer, 0.8 ul of 25× dNTPs, 2 ul of Random primers, 1 ul of Reverse Transcriptase, 1 ul of RNase inhibitor and 3.2 ul of H<sub>2</sub>O per reaction were added to 10 ul total RNA. cDNA was generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, Calif.) through the following steps: 25° C. 10 min, 37° C. 120 min, 85° C. 5 sec, 4° C. hold.

Real Time PCR:

2 ul of cDNA was added to a master mix containing 0.5 ul of GAPDH TaqMan Probe (Applied Biosystems Cat #4326317E), 0.5 ul of BCL11a TaqMan probe (Applied Biosystems cat #Hs01093198\_m1 or Hs01093199\_m1 or Hs00256254\_m1 or Hs00250581\_s1) and 5 ul of Lightcycler 480 probe master mix (Roche Cat #04887301001) per well in a 384 well 50 plate (Roche cat #04887301001). Real time PCR was done in an ABI 7900HT Real Time PCR system (Applied Biosystems) using the ΔΔCt(RQ) assay. Each duplex was tested in two independent transfections and each transfection was assayed in duplicate.

To calculate relative fold change in BCL11a expression, real time PCR data were analyzed using the ΔΔCt method and normalized to assays performed with cells transfected with 10 nM of the control siRNA AD-1955, or mock transfected cells. IC50s were calculated using a 4 parameter fit model using XLFit and normalized to cells transfected with AD-1955 over the same dose range, or to its own lowest dose.

TaqMan probes that recognize BCL11a and the RefSeq gene models they are predicted to detect are included in Table 8. Yes, indicates that the probe is expected to detect the isoform; No, indicates that the probe is not expected to detect the isoform; and Long, indicates that the RefSeq model contains the form of BCL11a with a long version of exon 4.

TABLE 8

BCL11a TaqMan probe specificity.				
	Hs01093199_m1	Hs01093198_m1	Hs00250581_s1*	Hs00256254_m1
NM_018014.3 (long) (SEQ ID NO: 4)	Yes	No	No	Yes
NM_138559.1 (SEQ ID NO: 5)	No	Yes	No	Yes
NM_022893.3 (long) (SEQ ID NO: 3)	No	No	Yes	Yes

out the process). Ten microliters of magnetic beads and 80 ul Lysis/Binding Buffer mixture were added to a round bottom plate and mixed for 1 minute. Magnetic beads were captured using magnetic stand and the supernatant was removed without disturbing the beads. After removing the supernatant, the lysed cells were added to the remaining beads and mixed for 5 minutes. After removing supernatant, magnetic beads were washed twice with 150 ul Wash Buffer A and mixed for 1 minute. Beads were captured again and the supernatant removed. Beads were then washed with 150 ul Wash Buffer B, captured and the supernatant removed. Beads were next washed with 150 ul Elution Buffer, captured and the supernatant removed. Beads were allowed to dry for 2 minutes. After drying, 50 ul of Elution Buffer was added and mixed for 5 minutes at 70° C. Beads were captured on a magnet for 5 minutes. 40 ul of the supernatant was removed and added to another 96 well plate.

Exogenous Screening:

siRNA mediated knockdown of BCL11a was also screened in an exogenous assay using an expression clone purchased from Origene (CAT# RC205816) containing the BCL11a sequence corresponding to NM\_018014.2 and neomycin (Neo), which was used for normalization. Cos7 cells were sequentially transfected with 1 ng, 15 ng or 30 ng of the BCL11a plasmid and each of the siRNAs so that the final siRNA concentration was 50 nM. For transfection, 0.5 ul of Lipofectamine 2000 (Invitrogen) was mixed with 14.5 ul of Opti-MEM and 5 ul of plasmid to make a final plasmid concentration of 1, 15, or 30 ng/well. 20 ul of the mixture was distributed to each well of a 96 well plate and 80 ul of media containing ~2×10<sup>4</sup> Cos7 cells was then added. After 4 hours, the media was removed and cells were retransfected with siRNA to give a final concentration of 50 nM. siRNA trans-

## 105

fection was performed as described above. After 24 hrs, the cells were harvested and prepared as described and analyzed as above for qPCR except that Neo, rather than GAPDH was used as the endogenous control gene to control for plasmid copy number. Expression of each transcript was quantified using qPCR with gene specific BCL11a and Neomycin TaqMan probes (Hs00256254\_m1 and Table 9). Table 10 includes the sequence of the primers and probes that made up the TaqMan assay used to detect Neo used as an endogenous control in the experiment.

TABLE 9

Neomycin TaqMan assay sequence.	
Forward Primer:	Neo F1
Forward	TATTGCTGAAGAGCTTGG
Primer Sequence:	
Forward	525
Primer SEQ ID NO.:	
Reverse Primer:	Neo R1
Reverse	GTCAAGAAGGCGATAGAA
Primer Sequence:	
ReversePrimer	256
SEQ ID NO.:	
TaqMan Probe:	Neo TP1
TaqMan	TAAAGCACGAGGAAGCGG
Probe Sequence:	
TaqMan Probe	527
SEQ ID NO.:	

In vitro Knockdown of Endogenous BCL11a Expression by BCL11a siRNA Duplexes.

Table 10 illustrates the knockdown of BCL11a in the two cell lines, H441 and WI-38, by BCL11a modified siRNA duplexes (Table 3 and Table 5). Silencing is expressed as the fraction RNA message remaining relative to the negative (luciferase) control siRNA AD-1955. Data were generated as described above following transfection of 10 nM of each siRNA. qPCR was run using the BCL11a TaqMan probe Hs00256254\_m1.

TABLE 10

BCL11a expression in single dose screen in H441 and WI-38 cell lines.		
Duplex Name	H441	WI-38
AD-46498.1	0.89	1.74
AD-46500.1	0.87	1.08
AD-46501.1	1.01	1.28
AD-46502.1	0.51	0.62
AD-46503.1	0.43	0.62
AD-46504.1	0.74	0.85
AD-46505.1	0.82	1.07
AD-46506.1	0.71	0.62
AD-46507.1	0.59	0.67
AD-46508.1	0.71	0.81
AD-46509.1	0.3	0.34
AD-46510.1	0.88	1.06
AD-46511.1	0.93	0.92
AD-46512.1	0.88	1.01
AD-46513.1	0.79	1.14
AD-46514.1	0.75	0.68
AD-46515.1	0.55	0.56
AD-46516.1	0.79	0.95
AD-46517.1	0.83	0.81
AD-46518.1	0.78	0.89
AD-46519.1	0.94	0.79
AD-46520.1	0.7	0.71
AD-46521.1	0.66	0.67
AD-46522.1	0.43	0.71
AD-46523.1	0.51	0.62

## 106

TABLE 10-continued

BCL11a expression in single dose screen in H441 and WI-38 cell lines.		
Duplex Name	H441	WI-38
AD-46524.1	0.89	1.02
AD-46525.1	0.5	0.54
AD-46526.1	0.71	0.58
AD-46527.1	0.83	0.68
AD-46528.1	0.93	0.95
AD-46529.1	0.82	0.85
AD-46530.1	0.89	0.92
AD-46531.1	0.74	0.57
AD-46532.1	0.49	0.56
AD-46533.1	0.55	0.5
AD-46534.1	0.83	0.74
AD-46535.1	0.44	0.63
AD-46536.1	0.53	0.88
AD-46537.1	0.81	0.8
AD-46538.1	0.61	0.65
AD-46539.1	0.69	0.57
AD-46540.1	0.61	0.63
AD-46541.1	0.8	0.68
AD-46542.1	0.76	0.77
AD-46543.1	0.54	0.61
AD-1955	0.92	0.87
AD-1955	0.95	0.9
AD-1955	0.96	0.95
AD-1955	0.97	0.96
AD-1955	0.98	1
AD-1955	0.99	1
AD-1955	1.1	1.1
AD-1955	1.16	1.27

In vitro Knockdown of the Long Form of BCL11a by BCL11a siRNA Duplexes.

In order to identify siRNAs that can specifically silence the long form of BCL11a; Hep3B cells were transfected with BCL11a modified siRNA duplexes (Table 3 and Table 5), processed as described above for qPCR, and probed with each of the 4 TaqMan probes in Table 8. Silencing of BCL11a by the siRNA duplex is expressed as the fraction RNA message remaining relative to the negative control siRNA AD-1955 (Table 11). As illustrated in Table 11, the siRNAs that show silencing when probed with TaqMan probe Hs01093199\_m1 are specific for exon 4 long form.

TABLE 11

BCL11a expression in single dose screen to identify siRNAs that target transcripts with the long form of exon 4.				
Duplex ID	10 nM Avg	10 nM STDEV	0.1 nM Avg	0.1 nM STDEV
Probe Hs01093198_m1				
AD-52060.1	1.06	0.12	1.11	0.06
AD-52061.1	0.79	0.05	0.88	0.00
AD-52062.1	1.10	0.08	1.01	0.12
AD-52063.1	0.98	0.11	1.00	0.06
AD-52064.1	0.95	0.00	1.03	0.07
AD-52065.1	1.18	0.04	1.05	0.07
AD-52066.1	0.68	0.02	1.00	0.04
AD-52067.1	1.14	0.09	1.06	0.02
AD-52068.1	0.90	0.19	1.03	0.10
AD-52069.1	0.92	0.04	0.96	0.01
AD-52070.1	1.06	0.05	1.31	0.15
AD-52071.1	1.08	0.26	1.17	0.11
AD-52072.1	1.14	0.10	1.10	0.03
AD-52073.1	1.04	0.01	1.12	0.02
AD-52074.1	1.07	0.01	1.08	0.09
AD-52075.1	1.24	0.04	1.17	0.05
AD-52076.1	1.02	0.12	1.03	0.05
AD-52077.1	0.77	0.34	1.29	0.07
AD-52078.1	1.03	0.10	1.13	0.03
AD-52079.1	1.15	0.13	0.96	0.16

107

TABLE 11-continued

BCL11a expression in single dose screen to identify siRNAs that target transcripts with the long form of exon 4.				
Duplex ID	10 nM Avg	10 nM STDEV	0.1 nM Avg	0.1 nM STDEV
AD-52080.1	1.13	0.08	1.12	0.09
AD-52081.1	1.26	0.01	1.12	0.06
AD-52082.1	1.04	0.11	1.15	0.14
AD-52083.1	1.27	0.04	1.29	0.00
AD-52084.1	1.31	0.24	1.04	0.12
AD-52085.1	1.07	0.10	0.98	0.13
AD-52086.1	1.00	0.00	1.22	0.07
AD-52087.1	1.34	0.01	1.21	0.10
AD-52088.1	1.02	0.20	1.08	0.20
AD-52089.1	1.37	0.11	1.08	0.01
AD-52090.1	0.81	0.01	1.11	0.32
AD-52091.1	1.00	0.11	1.11	0.21
AD-52092.1	1.16	0.02	1.17	0.06
AD-52093.1	1.23	0.05	1.08	0.00
AD-52094.1	1.00	0.14	1.07	0.01
AD-52095.1	1.12	0.10	1.11	0.13
Probe Hs01093199_m1				
AD-52060.1	0.92	0.14	1.00	0.16
AD-52061.1	0.46	0.01	0.27	0.01
AD-52062.1	0.77	0.04	0.84	0.02
AD-52063.1	0.97	0.19	1.00	0.00
AD-52064.1	0.76	0.09	0.96	0.08
AD-52065.1	0.31	0.07	0.35	0.01
AD-52066.1	0.43	0.04	0.45	0.03
AD-52067.1	0.36	0.05	0.44	0.11
AD-52068.1	0.90	0.28	1.03	0.08
AD-52069.1	0.92	0.13	0.93	0.04
AD-52070.1	0.75	0.01	1.19	0.05
AD-52071.1	1.02	0.12	1.10	0.06
AD-52072.1	0.49	0.09	0.44	0.05
AD-52073.1	1.05	0.08	1.06	0.12
AD-52074.1	0.71	0.11	0.89	0.05
AD-52075.1	0.86	0.07	0.79	0.05
AD-52076.1	1.23	0.05	1.04	0.08
AD-52077.1	0.83	0.63	1.33	0.36
AD-52078.1	0.69	0.10	0.95	0.05
AD-52079.1	0.65	0.07	0.77	0.09
AD-52080.1	0.90	0.06	0.94	0.17
AD-52081.1	1.12	0.13	1.06	0.08
AD-52082.1	0.74	0.13	1.07	0.07
AD-52083.1	1.16	0.08	1.27	0.01
AD-52084.1	1.02	0.29	0.91	0.01
AD-52085.1	1.25	0.24	1.06	0.10
AD-52086.1	1.02	0.03	1.22	0.15
AD-52087.1	1.28	0.11	1.23	0.14
AD-52088.1	0.39	0.02	0.43	0.08
AD-52089.1	1.58	0.13	1.15	0.05
AD-52090.1	1.03	0.08	1.29	0.26
AD-52091.1	0.43	0.04	0.49	0.16
AD-52092.1	1.04	0.05	1.09	0.11
AD-52093.1	0.73	0.15	0.83	0.09
AD-52094.1	0.45	0.18	0.72	0.01
AD-52095.1	0.22	0.04	0.30	0.02
Probe Hs00256254_m1				
AD-52060.1	0.99	0.01	1.10	0.09
AD-52061.1	0.73	0.07	0.78	0.04
AD-52062.1	1.02	0.11	1.17	0.22
AD-52063.1	0.96	0.11	0.97	0.04
AD-52064.1	0.96	0.08	1.01	0.01
AD-52065.1	1.02	0.01	0.93	0.04
AD-52066.1	0.72	0.03	0.87	0.09
AD-52067.1	0.94	0.02	0.95	0.10
AD-52068.1	1.00	0.18	1.19	0.06
AD-52069.1	1.03	0.05	1.04	0.04
AD-52070.1	1.10	0.04	1.14	0.03
AD-52071.1	1.15	0.13	1.24	0.02
AD-52072.1	0.88	0.02	1.07	0.02
AD-52073.1	1.17	0.11	1.25	0.03
AD-52074.1	1.04	0.03	1.03	0.11
AD-52075.1	1.34	0.01	1.12	0.11
AD-52076.1	1.17	0.01	1.12	0.06
AD-52077.1	1.19	0.07	1.22	0.14
AD-52078.1	1.11	0.03	1.19	0.04

108

TABLE 11-continued

BCL11a expression in single dose screen to identify siRNAs that target transcripts with the long form of exon 4.				
Duplex ID	10 nM Avg	10 nM STDEV	0.1 nM Avg	0.1 nM STDEV
AD-52079.1	1.13	0.04	1.17	0.16
AD-52080.1	1.20	0.04	1.11	0.05
AD-52081.1	1.08	0.08	1.15	0.03
AD-52082.1	1.13	0.07	1.13	0.06
AD-52083.1	1.33	0.01	1.22	0.01
AD-52084.1	1.13	0.03	1.12	0.03
AD-52085.1	1.10	0.04	1.08	0.04
AD-52086.1	1.11	0.06	1.15	0.02
AD-52087.1	1.41	0.15	1.14	0.02
AD-52088.1	0.87	0.11	0.90	0.12
AD-52089.1	1.21	0.05	1.26	0.03
AD-52090.1	1.39	0.07	1.41	0.12
AD-52091.1	0.90	0.07	1.00	0.02
AD-52092.1	1.32	0.30	1.21	0.08
AD-52093.1	1.04	0.08	1.10	0.00
AD-52094.1	0.88	0.09	1.10	0.16
AD-52095.1	0.93	0.04	0.97	0.09
Probe Hs00250581_s1				
AD-52060.1	0.93	0.13	1.13	0.22
AD-52061.1	1.06	0.05	0.85	0.04
AD-52062.1	0.91	0.10	1.05	0.37
AD-52063.1	0.82	0.36	0.94	0.12
AD-52064.1	0.99	0.08	1.00	0.12
AD-52065.1	0.78	0.02	0.86	0.01
AD-52066.1	0.84	0.02	0.90	0.01
AD-52067.1	0.89	0.03	0.94	0.12
AD-52068.1	1.16	0.12	1.38	0.25
AD-52069.1	1.27	0.15	1.08	0.01
AD-52070.1	1.06	0.05	1.24	0.00
AD-52071.1	1.39	0.03	1.37	0.09
AD-52072.1	0.94	0.00	0.98	0.02
AD-52073.1	1.22	0.14	1.39	0.10
AD-52074.1	1.01	0.08	0.98	0.02
AD-52075.1	1.38	0.03	1.23	0.15
AD-52076.1	1.36	0.10	1.37	0.11
AD-52077.1	1.60	0.19	1.33	0.15
AD-52078.1	1.19	0.14	1.21	0.04
AD-52079.1	1.10	0.09	1.43	0.46
AD-52080.1	1.20	0.04	1.28	0.05
AD-52081.1	1.01	0.11	1.30	0.18
AD-52082.1	1.26	0.01	1.29	0.01
AD-52083.1	1.57	0.04	1.42	0.06
AD-52084.1	1.06	0.03	1.15	0.03
AD-52085.1	1.32	0.26	1.20	0.03
AD-52086.1	1.32	0.00	1.42	0.14
AD-52087.1	1.61	0.17	1.28	0.02
AD-52088.1	0.88	0.07	0.94	0.18
AD-52089.1	1.43	0.01	1.41	0.02
AD-52090.1	2.65	0.04	1.93	0.12
AD-52091.1	1.04	0.15	1.02	0.02
AD-52092.1	1.31	0.20	1.29	0.09
AD-52093.1	1.29	0.04	1.27	0.10
AD-52094.1	1.12	0.16	1.34	0.09
AD-52095.1	0.82	0.08	0.74	0.18

In vitro Knockdown of Exogenously Expressed BCL11a by BCL11a siRNA Duplexes.

Table 12 illustrates the knockdown of exogenously expressed BCL11a in the COST cell line, by BCL11a modified siRNA duplexes (Table 3 and Table 5). Silencing is expressed as the fraction mRNA message remaining relative to the negative control siRNA AD-1955. Data were generated as described above following transfection of 50 nM of each siRNA.

TABLE 12

Single siRNA dose knockdown of exogenously expressed BCL11a in Cos7 cells.						
Duplex Name	Ave 50 nM siRNA/30 ng BCL11a plasmid	SD 30 ng	Ave 50 nM siRNA/15 ng BCL11a plasmid	SD 15 ng	Ave 50 nM siRNA/15 ng BCL11a plasmid	SD 1 ng
AD-46498.1	0.58	0.02	0.64	0.09	0.88	0.62
AD-46500.1	0.77	0.07	0.78	0.14	0.94	0.31
AD-46501.1	0.81	0.03	0.74	0.04	1.11	0.23
AD-46502.1	0.26	0.03	0.30	0.05	0.36	0.13
AD-46503.1	0.25	0.01	0.29	0.04	0.28	0.06
AD-46504.1	0.56	0.09	0.45	0.01	0.46	0.08
AD-46505.1	0.73	0.03	0.64	0.03	0.95	0.27
AD-46506.1	0.59	0.03	0.68	0.03	0.67	0.08
AD-46507.1	0.24	0.03	0.30	0.01	0.51	0.09
AD-46508.1	0.56	0.01	0.68	0.08	0.98	0.17
AD-46509.1	0.20	0.02	0.26	0.01	0.29	0.00
AD-46510.1	0.70	0.04	0.71	0.25	0.49	0.20
AD-46511.1	0.71	0.01	0.74	0.03	0.94	0.40
AD-46512.1	0.82	0.08	0.87	0.15	0.71	0.06
AD-46513.1	0.36	0.04	0.47	0.07	0.57	0.17
AD-46514.1	0.28	0.02	0.46	0.09	0.57	0.43
AD-46515.1	0.38	0.03	0.36	0.03	0.59	0.36
AD-46516.1	0.60	0.09	0.67	0.16	0.44	0.20
AD-46517.1	0.86	0.04	0.92	0.10	0.48	0.11
AD-46518.1	0.74	0.01	0.82	0.04	0.71	0.25
AD-46519.1	0.51	0.06	0.48	0.03	0.45	0.27
AD-46520.1	0.30	0.00	0.45	0.00	0.45	0.02
AD-46521.1	0.44	0.01	0.46	0.06	0.37	0.03
AD-46522.1	0.23	0.03	0.28	0.00	1.36	1.54
AD-46523.1	0.39	0.07	0.36	0.02	0.39	0.05
AD-46524.1	0.69	0.09	0.74	0.15	0.77	0.00
AD-46525.1	0.27	0.03	0.34	0.04	0.68	0.15
AD-46526.1	0.27	0.02	0.30	0.01	0.41	0.02
AD-46527.1	0.83	0.25	0.67	0.13	0.68	0.26
AD-46528.1	0.99	0.22	0.78	0.06	0.62	0.28
AD-46529.1	0.52	0.42	0.33	0.07	0.38	0.11
AD-46530.1	0.88	0.05	0.82	0.01	0.46	0.02
AD-46531.1	0.59	0.10	0.63	0.05	0.60	0.11
AD-46532.1	0.61	0.54	0.29	0.06	0.34	0.08
AD-46533.1	0.39	0.05	0.39	0.06	0.35	0.07
AD-46534.1	0.67	0.04	0.78	0.11	0.67	0.15
AD-46535.1	0.30	0.04	0.28	0.03	0.21	0.06
AD-46536.1	0.24	0.05	0.25	0.01	0.67	0.56
AD-46537.1	0.40	0.05	0.51	0.06	0.61	0.08
AD-46538.1	0.35	0.09	0.42	0.03	0.31	0.08
AD-46539.1	0.49	0.03	0.44	0.01	0.63	0.45
AD-46540.1	0.42	0.04	0.39	0.07	0.55	0.22
AD-46541.1	0.75	0.03	0.71	0.03	0.87	0.23
AD-46542.1	0.37	0.01	0.36	0.02	0.39	0.09
AD-46543.1	0.26	0.01	0.30	0.02	0.34	0.11

IC<sub>50</sub> of Select BCL11a siRNA Duplexes in in vitro Screen.

Tables 13-14 and FIGS. 9A-9D illustrate the IC<sub>50</sub> of select BCL11a duplexes determined from the knockdown of exogenously expressed BCL11a in the COST cell line, by BCL11a modified siRNA duplexes (Table 3 and Table 5). Data were generated as described above following transfection of each siRNA duplex. Silencing of BCL11a is expressed as the fraction mRNA message remaining relative to the negative control siRNA AD-1955 (Table 13 and FIGS. 9A-9B) or to that of the lowest tested siRNA dose (Table 14 and FIGS. 9C-9D). IC<sub>50</sub> plots are an average of 2 biological replicates. As illustrated in Tables 13-14 and FIGS. 9A-9D, the majority of BCL11a siRNA duplexes knocked down BCL11a gene expression even at the lowest tested siRNA dose.

TABLE 13

IC <sub>50</sub> of select BCL11a siRNA duplexes normalized to AD-1955.	
Duplex Tested	IC50: in [nM] Normalized to AD-1955
AD-46536.1	0.002
AD-46535.1	0.003

TABLE 13-continued

IC <sub>50</sub> of select BCL11a siRNA duplexes normalized to AD-1955.	
Duplex Tested	IC50: in [nM] Normalized to AD-1955
AD-46509.1	0.004
AD-46529.1	0.004
AD-46503.1	0.009
AD-46525.1	0.009
AD-46502.1	0.016
AD-46523.1	0.016
AD-46543.1	0.024
AD-46515.1	0.038
AD-46532.1	0.038
AD-46542.1	0.057
AD-46522.1	0.069
AD-46533.1	0.069
AD-46538.1	0.096
AD-46507.1	1.166
AD-46526.1	1.166

111

TABLE 14

IC <sub>50</sub> of select BCL11a siRNA duplexes normalized to the lowest tested BCL11a siRNA dose.	
Duplex Tested	IC <sub>50</sub> : in [nM] normalized to Lowest Dose
AD-46509.1	0.009
AD-46503.1	0.020
AD-46525.1	0.030
AD-46502.1	0.043
AD-46543.1	0.120
AD-46535.1	0.144
AD-46522.1	0.144
AD-46542.1	0.173
AD-46523.1	0.260
AD-46515.1	0.304
AD-46526.1	0.602
AD-46529.1	0.627
AD-46532.1	1.118
AD-46507.1	1.730
AD-46533.1	1.037
AD-46536.1	6.153
AD-46538.1	#Intersect

Efficacy of Select BCL11a siRNA Duplexes in in vitro Screen.

Table 15 illustrates the efficacy of select BCL11a siRNA duplexes determined as described above. Silencing of BCL11a is expressed as the fraction mRNA message remaining relative to the negative control siRNA AD-1955 (Table 15).

TABLE 15

Efficacy of select BCL11a siRNA duplexes in in vitro screen.					
Duplex ID	Efficacy data				Dose response
	10 nM Avg	10 nM SD	0.1 nM Avg	0.1 nM SD	
AD-46509.6	0.18	0.02	0.25	0.02	0.025
AD-53263.1	0.53	0.09	0.82	0.13	
AD-53264.1	0.50	0.07	0.66	0.13	

112

TABLE 15-continued

Efficacy of select BCL11a siRNA duplexes in in vitro screen.					
Duplex ID	Efficacy data				Dose response
	10 nM Avg	10 nM SD	0.1 nM Avg	0.1 nM SD	
AD-53268.1	0.25	0.01	0.36	0.07	0.120
AD-53269.1	0.63	0.09	0.79	0.06	
AD-53270.1	0.51	0.11	0.73	0.11	
AD-53275.1	0.26	0.06	0.51	0.10	0.505
AD-53276.1	0.68	0.03	0.84	0.05	
AD-53279.1	0.77	0.08	1.02	0.03	
AD-53280.1	0.32	0.08	0.64	0.20	0.664
AD-53281.1	0.53	0.05	0.73	0.14	
AD-53285.1	0.48	0.06	0.83	0.05	
AD-53286.1	0.58	0.05	0.82	0.21	
AD-53287.1	0.81	0.07	0.92	0.07	
AD-53291.1	0.64	0.05	0.81	0.05	
AD-53292.1	0.50	0.01	0.75	0.18	
AD-53296.1	0.58	0.05	0.76	0.15	
AD-53297.1	0.67	0.08	0.76	0.12	
AD-53302.1	0.51	0.08	0.74	0.05	
AD-53303.1	0.83	0.05	1.11	0.20	
AD-1955 naive	1.00	0.00			
	0.91	0.09			

Selected exemplary siRNA duplexes showing inhibitory activities included:

For inhibition of human KLF1, AD-46095 showed an IC<sub>50</sub> of 36 pM.

TABLE 15A

The sequences of selected sense and antisense unmodified duplexes are as follows:						
Duplex ID	SEQ ID NO:	Sense	Position at 5' end of SEQ ID		Antisense	SEQ ID NO:
			NO: 1			
AD-46095.1	89	CCUUAUUGUGGCUGAUUU	1550-1568		AAUAUCAGCCACAAUAGG	90
AD-46134.1	55	UGUCCAACUGUCGUGCAA	1394-1412		UUGCACGACAGUUUGGACA	56
AD-46115.1	33	UGGUUUUCCACGAAUGGA	1251-1269		UCCAUUCGUGGAAAACCA	34
AD-46112.1	79	GCUCCUGAAGGUCCCUAU	1537-1555		AUAAGGGACCUUCAGGAGC	80
AD-46111.1	63	UGAGACAGACCGCCAAUA	1419-1437		UAUUUGGCGGUCUGUCUCA	64

TABLE 15B

Corresponding modified duplex sequences					
Duplex ID	SEQ ID NO:	Sense	Position at 5' end of SEQ ID NO: 1	Antisense	SEQ ID NO:
AD-46095.1	558	ccuuAuGuGGcuGAuAuudTsdT	1550-1568	AAuAUcAGCcAcAAuAAGGdTsdT	559
AD-46134.1	614	uGuccAAAcuGucGuGcAAdTsdT	1394-1412	UUGcACGAcAGUUUGGAcAdTsdT	615
AD-46115.1	612	uGGuuuucccAcGAuGGAdTsdT	1251-1269	UCCAUUCGUGGGAAAACcAdTsdT	613
AD-46112.1	586	GcuccuGAAGGucccuuAudTsdT	1537-1555	AuAAGGGACCUUcAGGAGCdTsdT	587
AD-46111.1	604	uGAGAcAGAccGccAAuAdTsdT	1419-1437	uAUUUGGCGGUCUGUCUcAdTsdT	605

For inhibition of human and mouse BCL11a, AD-46509 showed an IC<sub>50</sub> of 4 pM.

The sequences of selected sense and antisense unmodified duplexes are as follows:

Positions are relative to NM\_022893.3 (SEQ ID NO:3).

TABLE 15C

Duplex ID	SEQ ID NO:	Sense	Position at 5' end of SEQ ID NO: 3	Antisense	SEQ ID NO:	Duplex ID
AD-46509.1	201	UUUAUCGAGCACAAACGGA	415-433	415	202	UCCGUUUGUGCUCGAUAAA
AD-46536.1	257	CCCGCAGGGUAAUUGUAAA	702-720	702	258	UUUACAAAUACCCUGCGGG
AD-46535.1	241	CAAACAGGAACACAUAGCA	594-612	594	242	UGCUAUGUGUCCUGUUUG
AD-46529.1	239	ACGUCAUCUAGAGGAAUUU	571-589	571	240	AAAUUCCUCUAGAUGACGU

Corresponding modified duplex sequences

TABLE 15D

Duplex ID	SEQ ID NO:	Sense	Position at 5' end of SEQ ID NO: 3	Antisense	SEQ ID NO:	Duplex ID
AD-46509.1	293	uuuAucGAGcAcAAAcGGAdTsdT	415-433	415	294	UCCGUUUGUGCUCGAuAAAdTsdT
AD-46535.1	331	cAAAcAGGAAcAcAuAGcAdTsdT	594-612	594	332	UGCuAUGUGUCCUGUUUGdTsdT
AD-46529.1	329	AcGucAucuAGAGGAAuuudTsdT	571-589	571	330	AAAUUCCUCuAGAUGACGUdTsdT

Additional selected duplexes include:

AD53268:

Modified Sense: SEQ ID NO:632

Unmodified Sense: SEQ ID NO:672

Modified Anti-sense: SEQ ID NO:633

Unmodified anti-sense: SEQ ID NO:673

AD-53275:

Modified Sense: SEQ ID NO:638

Unmodified sense: SEQ ID NO:679

Modified Anti-sense: SEQ ID NO:639

Unmodified anti-sense: SEQ ID NO:680

For inhibition of mouse KLF1, AD-46151 (sense sequence: cuuuccAGGuuccGAGucudTsdT, SEQ ID NO: 681, and antisense sequence AGACUCGGAACCUUG-GAAAGdTsdT, SEQ ID NO: 682) showed an IC<sub>50</sub> of 3 pM.

#### Example 4

#### In vitro Mouse Embryonic Hemoglobin Switching Post BCL11a Knockdown by BCL11a siRNA Duplex

In order to evaluate the effect of BCL11a siRNA-mediated silencing of BCL11a on embryonic hemoglobin switching, MEL cells were transfected with a BCL11a siRNA or control Luc siRNA. BCL11a siRNA duplexes were transfected at concentrations of 31 nM, 62 nM, 125 nM, or 500 nM, (using the AF-009 (also called LNP09) delivery vehicle). Twenty four hours post transfection the level of BCL11a expression was evaluated as described above. As illustrated in FIG. 10A, there was a dose dependent knockdown of BCL11a expression 24 hours post transfection with BCL11a siRNA. This knockdown of BCL11a expression correlated with increased expression of the mouse embryonic hemoglobin genes  $\epsilon\gamma$  and  $\text{bh1}$ , measured 72 hours post siRNA transfection (FIG. 10B).

## 115

In addition, mouse bone marrow progenitor cells were isolated by negative selection and cultured in erythroid differentiation media. The cells were subsequently transfected with 1  $\mu$ M BCL11a siRNA or control Luc siRNA using two separate siRNA delivery vehicles (AF-009 or AF-012 (also called LNP12)). Seventy-two and ninety-six hours post transfection, the level of BCL11a expression was evaluated as described above. As illustrated in FIG. 11A, knockdown of BCL11a expression at both 72 and 96 hours post transfection with BCL11a siRNA was observed. This knockdown of BCL11a expression correlated with increased expression of the mouse embryonic hemoglobin gene  $\epsilon\gamma$ , measured at both 72 and 96 hours post siRNA transfection (FIG. 11B).

## Example 5

## In vivo Detection of Mouse Embryonic Hemoglobin Switching

In addition, mouse embryonic hemoglobin switching can be detected in vivo. As shown in FIGS. 12A-12C, mouse adult globin (bmaj) was detected at the E16 developmental stage, and later developmental time points, including E18, as well as in the bone marrow. Bmaj is depicted in FIG. 12 as Hb beta. No significant expression was detected in the E12 developmental stage (FIG. 12A). However, embryonic globin  $\epsilon\gamma$  (eps) was only detected in E12 fetal liver samples. Embryonic globin  $\epsilon\gamma$  was no longer expressed in later developmental time points, including E16 and E18, nor in the mouse bone marrow (FIG. 12B). Embryonic globin bh1 was also detected at the E12 developmental stage and not in the mouse bone marrow or spleen (FIG. 12C). A schematic representation of the hemoglobin genes is depicted in FIG. 12E. These data demonstrate the ability to detect mouse embryonic hemoglobin switching in vivo.

## Example 6

## In vitro Screening of KLF siRNA Duplexes for KLF Knockdown Activity

KLF siRNA duplexes were screened for the ability to knockdown KLF expression in vitro. Knockdown of both endogenous and exogenously expressed KLF were evaluated. In vitro Screening:

## Cell Culture and Transfections:

Cos7 cells (ATCC, Manassas, Va.) were grown to near confluence at 37° C. in an atmosphere of 5% CO<sub>2</sub> in DMEM (ATCC) supplemented with 10% FBS, streptomycin, and glutamine (ATCC) before being released from the plate by trypsinization.

KLF1 was screened in an exogenous assay using an expression clone purchased from Origene (CAT# SC323869) containing the KLF1 sequence corresponding to NM\_006563.2 and neomycin, which was used for normalization. Cos7 cells were sequentially transfected with 15 ng or 30 ng of the KLF1 plasmid and each of the siRNAs so that the final siRNA concentration was 50 nM, 5 nM or 0.5 nM for efficacy screens and in 12, 3 fold dilutions between 50 nM and 300 pM for dose response screens. For transfection, 0.5  $\mu$ l of Lipofectamine 2000 (Invitrogen) was mixed with 14.5  $\mu$ l of Opti-MEM and 5  $\mu$ l of plasmid to reach the final plasmid concentration. 20  $\mu$ l of the mixture was distributed to each well of a 96 well plate and 80  $\mu$ l of media containing  $\sim 2 \times 10^4$  Cos7 cells was then added. After 4 hours, media was removed and cells were retransfected with siRNA. After 24 hrs, cells were harvested and prepared for qPCR.

## 116

Total RNA Isolation Using DYNABEADS® mRNA Isolation Kit (Invitrogen, Part #: 610-12):

Cells were harvested and lysed in 150  $\mu$ l of Lysis/Binding Buffer then mixed for 5 minute at 850 rpm using an Eppendorf® Thermomixer (the mixing speed was the same throughout the process). Ten microliters of magnetic beads and 80  $\mu$ l of Lysis/Binding Buffer mixture were added to a round bottom plate and mixed for 1 minute. Magnetic beads were captured using a magnetic stand and the supernatant was removed without disturbing the beads. After removing supernatant, the lysed cells were added to the remaining beads and mixed for 5 minutes. After removing supernatant, the magnetic beads were washed 2 times with 150  $\mu$ l Wash Buffer A and mixed for 1 minute. Beads were capture again and the supernatant removed. The beads were then washed with 150  $\mu$ l Wash Buffer B, captured and supernatant was removed. The beads were next washed with 150  $\mu$ l Elution Buffer, captured and supernatant removed. The beads were allowed to dry for 2 minutes. After drying, 50  $\mu$ l of Elution Buffer was added and mixed for 5 minutes at 70° C. Beads were captured on magnet for 5 minutes. 40  $\mu$ l of supernatant was removed and added to another 96 well plate.

cDNA Synthesis Using ABI High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, Calif., Cat #4368813):

A master mix of 2  $\mu$ l 10 $\times$  Buffer, 0.8  $\mu$ l 25 $\times$  dNTPs, 2  $\mu$ l Random primers, 1  $\mu$ l Reverse Transcriptase, 1  $\mu$ l RNase inhibitor and 3.2  $\mu$ l of H<sub>2</sub>O per reaction were added into 10  $\mu$ l total RNA. cDNA was generated using a Bio-Rad C-1000 or S-1000 thermal cycler (Hercules, Calif.) through the following steps: 25° C. 10 min, 37° C. 120 min, 85° C. 5 sec, 4° C. hold.

## Real Time PCR:

2  $\mu$ l of cDNA were added to a master mix containing 0.5  $\mu$ l Neo TaqMan Probe (Table 9), 0.5  $\mu$ l KLF1 TaqMan probe (Applied Biosystems cat #Hs00610592\_m1) and 5  $\mu$ l Lightcycler 480 probe master mix (Roche Cat #04887301001) per well in a 384 well 50 plates (Roche cat #04887301001). Real time PCR was done in an ABI 7900HT Real Time PCR system (Applied Biosystems) using the  $\Delta\Delta$ Ct(RQ) assay. Each duplex was tested in at least two independent transfections and each transfection was assayed in duplicate, unless otherwise noted in the summary tables.

To calculate relative fold change, real time data were analyzed using the  $\Delta\Delta$ Ct method and normalized to assays performed with cells transfected with AD-1955, or mock transfected cells. IC50s were calculated using a 4 parameter fit model using XLfit and normalized to cells transfected with AD-1955 over the same dose range, or to its own lowest dose. In vitro Efficacy of 19Mer KLF siRNA Duplexes for KLF Silencing Activity.

Table 16 illustrates the knockdown of KLF in COST cells transfected with 19mer modified siRNA duplexes targeting KLF (Table 2A-3). The data is expressed as a fraction of KLF message remaining in cells transfected with siRNAs targeting KLF, relative to cells transfected with a negative control siRNA, AD-1955. All siRNAs were transfected at least two times and qPCR reactions were performed in duplicate. Cos7 cells were sequentially transfected with 15 ng or 30 ng of the KLF1 plasmid and each of the siRNAs.

TABLE 16

19mer KLF siRNA duplex efficacy screen.		
Duplex ID	Avg fold change	STDEV
AD-46090.1	1	0.05
AD-46091.1	1.14	0.24
AD-46092.1	0.31	0.16

117

TABLE 16-continued

19mer KLF siRNA duplex efficacy screen.		
Duplex ID	Avg fold change	STDEV
AD-46093.1	0.79	0.22
AD-46094.1	1.08	0.23
AD-46095.1	0.18	0.09
AD-46096.1	0.99	0.53
AD-46097.1	1.32	0.32
AD-46098.1	0.36	0.15
AD-46099.1	1.01	0.3
AD-46100.1	0.49	0.16
AD-46101.1	0.64	0.1
AD-46102.1	1.14	0.7
AD-46103.1	1.23	0.29
AD-46104.1	0.51	0.13
AD-46105.1	0.33	0.12
AD-46106.1	0.66	0.22
AD-46107.1	0.75	0.05
AD-46108.1	0.33	0.1
AD-46109.1	0.59	0.22
AD-46110.1	0.19	0.1
AD-46111.1	0.19	0.05
AD-46112.1	0.21	0.11
AD-46113.1	0.58	0.23
AD-46114.1	0.93	0.14
AD-46115.1	0.18	0.06
AD-46116.1	0.41	0.14
AD-46117.1	0.25	0.09
AD-46118.1	0.53	0.21
AD-46119.1	0.92	0.13
AD-46120.1	1.18	0.86
AD-46121.1	0.75	0.11
AD-46122.1	0.83	0.42
AD-46123.1	0.34	0.07
AD-46124.1	0.91	0.37
AD-46125.1	0.65	0.15
AD-46126.1	0.41	0.12
AD-46127.1	0.57	0.12
AD-46128.1	0.36	0.12
AD-46129.1	0.77	0.18
AD-46130.1	0.66	0.37
AD-46132.1	0.57	0.1
AD-46133.1	0.47	0.07
AD-46134.1	0.19	0.05
AD-46135.1	0.54	0.03
AD-46136.1	0.45	0.2
AD-1955	1.03	0.02

IC<sub>50</sub> of Select 19Mer KLF siRNA Duplexes in in vitro Dose Response Screen.

Table 17 illustrates the IC<sub>50</sub> value of select 19mer KLF siRNA duplexes in in vitro dose response screen. 19mer KLF siRNA duplexes that were efficacious in the initial single dose screen (Table 16), were tested for KLF knockdown activity in a dose response. For normalization, knockdown of KLF was measured relative to the non-targeting control, AD-1955. Each siRNA duplex was screened in duplicate and an IC<sub>50</sub> calculated for each experiment (IC<sub>50A</sub> and IC<sub>50B</sub>), as well as an average IC<sub>50</sub> (Avg IC<sub>50</sub>).

TABLE 17

IC <sub>50</sub> of select 19mer KLF siRNA duplexes in in vitro dose response screen.			
Duplex ID	IC-50 A (nM)	IC-50 B (nM)	Avg IC50 (nM)
AD-46115.1	0.0767	0.3087	0.1648
AD-46111.1	0.1524	0.3724	0.2993
AD-46110.1	0.3455	1.935	0.9737
AD-46095.1	0.02	0.0588	0.0364
AD-46134.1	0.0234	0.1253	0.0684
AD-46112.1	0.4053	0.0638	0.2237
AD-46117.1	5.3373	0.2518	1.2338

118

In vitro Efficacy of 21/23Mer KLF siRNA Duplexes for KLF Silencing Activity.

Table 18 illustrates the knockdown of KLF in COST cells transfected with 21/23mer modified siRNA duplexes targeting KLF (Table 5). The data is expressed as a fraction of KLF message remaining in cells transfected with siRNAs targeting KLF, relative to cells transfected with a negative control siRNA, AD-1955. All siRNAs were transfected at least two times and qPCR reactions were performed in duplicate. Cos7 cells were sequentially transfected with 15 ng or 30 ng of the KLF1 plasmid and each of the siRNAs so that the final siRNA concentration was 50 nM, 5 nM or 0.5 nM

TABLE 18

21/23mer KLF siRNA duplex efficacy screen.						
Duplex ID	50 nM		5 nM		0.5 nM	
	Avg	STDEV	Avg	STDEV	Avg	STDEV
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AD-53284.1	0.46	0.047	0.329	0.065	0.645	0.059
AD-53290.1	0.287	0.065	0.364	0.221	0.685	0.182
AD-53295.1	1.088	0.097	0.79	0.239	0.53	0.1
AD-53301.1	0.918	0.08	0.871	0.192	0.903	0.064
AD-53321.1	0.444	0.303	0.711	0.189	0.511	0.101
AD-53307.1	0.308	0.047	0.328	0.074	0.465	0.072
AD-53309.1	0.267	0.055	0.257	0.033	0.522	0.126
AD-53311.1	0.266	0.021	0.292	0.033	0.432	0.037
AD-53313.1	0.249	0.034	0.303	0.063	0.521	0.106
AD-53315.1	0.307	0.106	0.421	0.247	0.762	0.126
AD-53317.1	0.257	0.051	0.407	0.109	0.673	0.116
AD-53319.1	0.236	0.066	0.236	0.081	0.573	0.212
AD-53322.1	0.461	0.155	0.286	0.163	0.296	0.043
AD-53308.1	0.24	0.017	0.338	0.045	0.433	0.045
AD-53310.1	0.249	0.013	0.314	0.061	0.497	0.093
AD-53312.1	0.23	0.021	0.251	0.019	0.499	0.056
AD-53314.1	0.237	0.047	0.274	0.058	0.476	0.075
AD-53316.1	0.296	0.129	0.571	0.168	0.657	0.19
AD-53318.1	0.381	0.051	0.414	0.09	0.786	0.107
AD-53320.1	0.274	0.05	0.42	0.136	0.477	0.124
AD-1955	1.01	0.14				
Mock	0.98	0.19				

## Example 7

In vitro Mouse Embryonic Hemoglobin Switching Post KLF1 Knockdown by KLF1 siRNA Duplex

In order to evaluate the effect of KLF1 siRNA mediated silencing of KLF1 on embryonic hemoglobin switching, MEL cells were transfected with a KLF1 siRNA or control Luc siRNA. KLF1 siRNA duplexes were transfected at concentrations of 12.5 nM, 25 nM, 50 nM, 100 nM, or 200 nM (using the AF-009 delivery vehicle). Twenty four hours post transfection the level of KLF1 expression was evaluated as described above. As illustrated in FIG. 13A, there was a dose dependent knockdown of KLF1 expression 24 hours post transfection with KLF1 siRNA. This knockdown of KLF1 expression correlated with increased expression of the mouse embryonic hemoglobin genes  $\epsilon\gamma$  and  $\beta h1$  measured 72 hours post siRNA transfection (FIG. 13B).

## Example 8

In vivo Detection of Selective Inhibition of mKLF mRNA in vivo

FIGS. 14A-14E further depict the selective inhibition of mKLF1 mRNA in the bone marrow and spleen in vivo, and

119

increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$ , using mKLF1 iRNA at a concentration of 3x1 mg/kg encapsulated in AF-012. A 95% reduction of mKLF1, normalized to GAPDH loading control, relative to luciferase, was detected in the treated bone marrow; a 75% reduction of mKLF1, normalized to GAPDH loading control, was detected in the treated spleen. Increased expression of mouse embryonic hemoglobin genes  $\epsilon\gamma$  in bone marrow (FIG. 14B) and spleen (FIG. 14D) is detected after treatment with

120

mKLF1 iRNA. FIG. 14E depicts a schematic representation of the hemoglobin genes.

## EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

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&lt;210&gt; SEQ ID NO 5

&lt;211&gt; LENGTH: 2358

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 5

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&lt;210&gt; SEQ ID NO 6

&lt;211&gt; LENGTH: 3425

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Mus musculus

&lt;400&gt; SEQUENCE: 6

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&lt;210&gt; SEQ ID NO 7

&lt;211&gt; LENGTH: 1825

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Mus musculus

&lt;400&gt; SEQUENCE: 7

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tgccattttt ttcattctct tctctccctc tatccctctt ctctcttctt ctctctcttt	120
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caaatacacg cttttggtga ctacc	1825

&lt;210&gt; SEQ ID NO 8

&lt;211&gt; LENGTH: 1480

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Mus musculus

&lt;400&gt; SEQUENCE: 8

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<210> SEQ ID NO 9  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 9

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<210> SEQ ID NO 10  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 10

ucucggagc gccaccacu	19
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<210> SEQ ID NO 11  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 11

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<210> SEQ ID NO 12  
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 <212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 12

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<210> SEQ ID NO 13
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 13

cgagacucug ggcgcgauau                               19

<210> SEQ ID NO 14
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 14

auaugcgccc agagucucg                               19

<210> SEQ ID NO 15
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 15

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<210> SEQ ID NO 16
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 16

ugauccucg aacccaaaa                               19

<210> SEQ ID NO 17
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 17

ucggagggauc acucggguu                               19

<210> SEQ ID NO 18
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 18

aaccgagug auccuccga                               19

<210> SEQ ID NO 19
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 19

uggcgugca accggugua                               19

<210> SEQ ID NO 20
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 20

uacaccguu gcagcgcca                               19

<210> SEQ ID NO 21
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 21

ccuccuuccu gaguuguuu                             19

<210> SEQ ID NO 22
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 22

aaacaacuca ggaaggagg                             19

<210> SEQ ID NO 23
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 23

aagcgaggcc gacguucgu                             19

<210> SEQ ID NO 24
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 24

acgaacgucg gccucgcuu 19

<210> SEQ ID NO 25  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 25

agcucugccc acgugcuuu 19

<210> SEQ ID NO 26  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 26

aaagcacgug ggcagagcu 19

<210> SEQ ID NO 27  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 27

gccuggcac uuggacucu 19

<210> SEQ ID NO 28  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 28

agaguccaag ugccagggc 19

<210> SEQ ID NO 29  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 29

uggcacuugg acucuccua 19

<210> SEQ ID NO 30  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 30

uaggagaguc caagugcca 19

<210> SEQ ID NO 31  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 31

ucuccuagug acuggggau 19

<210> SEQ ID NO 32  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 32

auccccaguc acuaggaga 19

<210> SEQ ID NO 33  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 33

ugguuuuucc acgaaugga 19

<210> SEQ ID NO 34  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 34

uccauucgug ggaaaacca 19

<210> SEQ ID NO 35  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 35

uuucccacga auggaccu 19

<210> SEQ ID NO 36  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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<400> SEQUENCE: 36

aggguccauu cgugggaaa 19

<210> SEQ ID NO 37  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 37

cuggacucgc guucccaa 19

<210> SEQ ID NO 38  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 38

uuugggaacg cgaguccag 19

<210> SEQ ID NO 39  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 39

caaagaacca cccaaauau 19

<210> SEQ ID NO 40  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 40

auauuugggu ggaucuuug 19

<210> SEQ ID NO 41  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 41

uaucaaacac ggacccaaua 19

<210> SEQ ID NO 42  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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<400> SEQUENCE: 42

uaugggucg uguuugaua

19

<210> SEQ ID NO 43

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 43

ucuuacggaa aaucgaca

19

<210> SEQ ID NO 44

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 44

ugucggauuu uccguaaga

19

<210> SEQ ID NO 45

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 45

cuuacggaaa auccgaca

19

<210> SEQ ID NO 46

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 46

uugucggauu uuccguaag

19

<210> SEQ ID NO 47

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 47

cggaaaaucc gacaagccu

19

<210> SEQ ID NO 48

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 48

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aggcuuugucg gauuuuccg 19

<210> SEQ ID NO 49  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 49

ggaaaauccg acaagccuu 19

<210> SEQ ID NO 50  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 50

aaggcuuguc ggauuuucc 19

<210> SEQ ID NO 51  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 51

gagaugucca aacugucgu 19

<210> SEQ ID NO 52  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 52

acgacaguuu ggacaucuc 19

<210> SEQ ID NO 53  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 53

auguccaaac ugucgugca 19

<210> SEQ ID NO 54  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 54

ugcacgacag uuuggacau

19

<210> SEQ ID NO 55

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 55

uguccaaaacu gucgugcaa

19

<210> SEQ ID NO 56

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 56

uugcacgaca guuuggaca

19

<210> SEQ ID NO 57

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 57

guccaaacug ucgugcaaa

19

<210> SEQ ID NO 58

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 58

uuugcacgac aguuuggac

19

<210> SEQ ID NO 59

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 59

aaacugucgu gcaaaccga

19

<210> SEQ ID NO 60

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 60

uggguuugca cgacaguuu

19

&lt;210&gt; SEQ ID NO 61

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 61

gugcaaacc agugagaca

19

&lt;210&gt; SEQ ID NO 62

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 62

ugucucacug gguuugcac

19

&lt;210&gt; SEQ ID NO 63

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 63

ugagacagac cgccaaaua

19

&lt;210&gt; SEQ ID NO 64

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 64

uauuuggcgg ucugucuca

19

&lt;210&gt; SEQ ID NO 65

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 65

gagacagacc gccaaauaa

19

&lt;210&gt; SEQ ID NO 66

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 66  
uuauuuggcg gucugucuc 19

<210> SEQ ID NO 67  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 67  
agacagaccg ccaauuaaa 19

<210> SEQ ID NO 68  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 68  
uuuauuuggc ggucugucu 19

<210> SEQ ID NO 69  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 69  
agaccgccaa auaaacgga 19

<210> SEQ ID NO 70  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 70  
uccguuuuuu uggcgguucu 19

<210> SEQ ID NO 71  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 71  
cgccaaauaa acggacuca 19

<210> SEQ ID NO 72  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 72  
ugaguccguu uauuuggcg 19

<210> SEQ ID NO 73  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 73  
aaaaaacgga cucagugga 19

<210> SEQ ID NO 74  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 74  
uccacugagu ccguuuauu 19

<210> SEQ ID NO 75  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 75  
gacucagugg acacucaga 19

<210> SEQ ID NO 76  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 76  
ucugaguguc cacugaguc 19

<210> SEQ ID NO 77  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 77  
cugggucuag aaagcggcu 19

<210> SEQ ID NO 78  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 78

agccgcuuuc uagaccag

19

&lt;210&gt; SEQ ID NO 79

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 79

gcuccugaag guccuuau

19

&lt;210&gt; SEQ ID NO 80

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 80

auaagggacc uucaggagc

19

&lt;210&gt; SEQ ID NO 81

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 81

cuccugaagg uccuuauu

19

&lt;210&gt; SEQ ID NO 82

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 82

aaauagggac cuucaggag

19

&lt;210&gt; SEQ ID NO 83

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 83

ccugaagguc ccuuauugu

19

&lt;210&gt; SEQ ID NO 84

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 84

acaauaaggg accuucagg

19

<210> SEQ ID NO 85

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 85

ucccuauug uggcugauu u

21

<210> SEQ ID NO 86

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 86

aaauacagcc acaauaaggg acc

23

<210> SEQ ID NO 87

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 87

cccuauugu ggcugauu

19

<210> SEQ ID NO 88

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 88

auaucagcca caauaaggg

19

<210> SEQ ID NO 89

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 89

ccuuauugug gcugauuu

19

<210> SEQ ID NO 90

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 90

aaauaucagcc acaauaagg

19

<210> SEQ ID NO 91

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 91

uguggcugau auuaacugu

19

<210> SEQ ID NO 92

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 92

acaguuaaua ucagccaca

19

<210> SEQ ID NO 93

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 93

caaugguuau ggguccuau

19

<210> SEQ ID NO 94

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 94

auaggaccca uaaccauug

19

<210> SEQ ID NO 95

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 95

aaugguuaug gguccuaua

19

<210> SEQ ID NO 96

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 96

uauaggaccc auaaccauu

19

<210> SEQ ID NO 97

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 97

augguuaugg guccuauaa

19

<210> SEQ ID NO 98

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 98

uuauaggacc cauaaccau

19

<210> SEQ ID NO 99

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 99

ugguuauggg uccuauaaa

19

<210> SEQ ID NO 100

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 100

uuuauaggac ccauaacca

19

<210> SEQ ID NO 101

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 101

gguaaugggu ccuaaaaaa

19

<210> SEQ ID NO 102

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 102

uuuuauagga cccauaacc 19

<210> SEQ ID NO 103

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 103

gagcccucca agaaacuuu 19

<210> SEQ ID NO 104

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 104

aaaguuuuu ggagggcuc 19

<210> SEQ ID NO 105

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 105

gaaacuuucc uagccucau 19

<210> SEQ ID NO 106

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 106

augaggcuag gaaaguuuc 19

<210> SEQ ID NO 107

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 107

ccucauagcc caugaggca 19

<210> SEQ ID NO 108

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 108
ugccucaugg gcuaugagg                                     19

<210> SEQ ID NO 109
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 109
gcugagacug ucuuacccu                                     19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 110
aggguaagac agucucagc                                     19

<210> SEQ ID NO 111
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 111
gagacugucu uaccucca                                     19

<210> SEQ ID NO 112
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 112
uggaggguaa gacagucuc                                     19

<210> SEQ ID NO 113
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 113
gaggacuucc ucaaguggu                                     19

<210> SEQ ID NO 114
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

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&lt;400&gt; SEQUENCE: 114

accacuugag gaaguccuc

19

&lt;210&gt; SEQ ID NO 115

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 115

gucugaggag acgcaggau

19

&lt;210&gt; SEQ ID NO 116

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 116

auccugcguc uccucagac

19

&lt;210&gt; SEQ ID NO 117

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 117

cgucccauca cgugagucu

19

&lt;210&gt; SEQ ID NO 118

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 118

agacucacgu gaugggacg

19

&lt;210&gt; SEQ ID NO 119

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 119

cccaucacgu gagucugaa

19

&lt;210&gt; SEQ ID NO 120

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 120

uucagacuca cgugauggg

19

&lt;210&gt; SEQ ID NO 121

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 121

ccaucacgug agucugaaa

19

&lt;210&gt; SEQ ID NO 122

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 122

uuucagacuc acgugaugg

19

&lt;210&gt; SEQ ID NO 123

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 123

cugaaaucgg aggacccuu

19

&lt;210&gt; SEQ ID NO 124

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 124

aaggguccuc cgauuucag

19

&lt;210&gt; SEQ ID NO 125

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 125

gaugagaggg acgugaccu

19

&lt;210&gt; SEQ ID NO 126

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 126

aggucacguc ccucucauc 19

<210> SEQ ID NO 127  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 127

gcgugggacc cggauuuu 19

<210> SEQ ID NO 128  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 128

aaagauccgg gucccacgc 19

<210> SEQ ID NO 129  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 129

cgugggaccc ggaucuuuu 19

<210> SEQ ID NO 130  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 130

aaaagaucgg ggucccacg 19

<210> SEQ ID NO 131  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 131

cccggauuuu uuccuuaca 19

<210> SEQ ID NO 132  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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<400> SEQUENCE: 132  
uguaaggaaa agauccggg 19

<210> SEQ ID NO 133  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 133  
ccggaucuuu uccuuacaa 19

<210> SEQ ID NO 134  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 134  
uuguaaggaa aagauccgg 19

<210> SEQ ID NO 135  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 135  
cggaucuuuu ccuuacaaa 19

<210> SEQ ID NO 136  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 136  
uuuguaagga aaagauccg 19

<210> SEQ ID NO 137  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 137  
caaacuucc agguuccga 19

<210> SEQ ID NO 138  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 138

ucggaaccug gaaaguuug

19

&lt;210&gt; SEQ ID NO 139

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 139

cuuuccaggu uccgagucu

19

&lt;210&gt; SEQ ID NO 140

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 140

agacucggaa ccuggaaag

19

&lt;210&gt; SEQ ID NO 141

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 141

ggccaguggc acaguucga

19

&lt;210&gt; SEQ ID NO 142

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 142

ucgaacugug ccacugggc

19

&lt;210&gt; SEQ ID NO 143

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 143

cuuccuucuu gaauugucu

19

&lt;210&gt; SEQ ID NO 144

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 144

agacaaauca agaaggaag

19

<210> SEQ ID NO 145

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 145

cagccggcga acuuuggca

19

<210> SEQ ID NO 146

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 146

ugccaaaguu cgccggcug

19

<210> SEQ ID NO 147

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 147

ggcgaacuuu ggcaccuaa

19

<210> SEQ ID NO 148

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 148

uuaggugcca aaguucgcc

19

<210> SEQ ID NO 149

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 149

cgaacuuugg caccuaaga

19

<210> SEQ ID NO 150

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 150

ucuuaggugc caaaguucg

19

<210> SEQ ID NO 151

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 151

gcucgcucag acgaacuga

19

<210> SEQ ID NO 152

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 152

ucaguucguc ugagcgagc

19

<210> SEQ ID NO 153

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 153

gaagcacacu ggacaucgu

19

<210> SEQ ID NO 154

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 154

acgaugucca gugugcuuc

19

<210> SEQ ID NO 155

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 155

gccucugccc acgugcuuu

19

<210> SEQ ID NO 156

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 156  
aaagcacgug ggcagagggc 19

<210> SEQ ID NO 157  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 157  
cugaccacuu agcucugca 19

<210> SEQ ID NO 158  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 158  
ugcagagcua aguggucag 19

<210> SEQ ID NO 159  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 159  
cacuuagcuc ugcacauga 19

<210> SEQ ID NO 160  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 160  
ucaugugcag agcuaagug 19

<210> SEQ ID NO 161  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 161  
caaggacugg ggaugaaa 19

<210> SEQ ID NO 162  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 162

auuucaucucc caguccuug

19

<210> SEQ ID NO 163

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 163

cuggggauga aauaagagu

19

<210> SEQ ID NO 164

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 164

acucuauuuu cauccccag

19

<210> SEQ ID NO 165

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 165

ggaugaaaua agaguggau

19

<210> SEQ ID NO 166

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 166

auccacucuu auuucaucc

19

<210> SEQ ID NO 167

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 167

guggauccaa ggaccguau

19

<210> SEQ ID NO 168

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 168

auacgguccu uggauccac

19

<210> SEQ ID NO 169

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 169

ccaaggaccg uaucccaaa

19

<210> SEQ ID NO 170

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 170

uuugggauac gguccuugg

19

<210> SEQ ID NO 171

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 171

ccaaaagaug ggccauuau

19

<210> SEQ ID NO 172

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 172

auaauggccc aucuuuugg

19

<210> SEQ ID NO 173

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 173

gggccauuau auaguccua

19

<210> SEQ ID NO 174

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 174

uaggacuaua uaauggccc

19

<210> SEQ ID NO 175

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 175

cauuauauag uccuaccca

19

<210> SEQ ID NO 176

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 176

uggguaggac uauuaaag

19

<210> SEQ ID NO 177

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 177

cagaagacca uacaaagga

19

<210> SEQ ID NO 178

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 178

uccuuuguau ggucuucug

19

<210> SEQ ID NO 179

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 179

gagccuucag gacaaaccu

19

<210> SEQ ID NO 180

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 180

agguuugucc ugaaggcuc

19

<210> SEQ ID NO 181

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 181

caggacaaac cucacaugu

19

<210> SEQ ID NO 182

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 182

acaugugagg uuuguccug

19

<210> SEQ ID NO 183

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 183

gacccagcaa uauagacca

19

<210> SEQ ID NO 184

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 184

uggucuauau ugcuggguc

19

<210> SEQ ID NO 185

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 185

caccagauaa aucaacuca

19

<210> SEQ ID NO 186

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 186

ugaguugauu uaucuggug

19

<210> SEQ ID NO 187

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 187

gauggacugg ggugagauu

19

<210> SEQ ID NO 188

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 188

aaucacccc caguccauc

19

<210> SEQ ID NO 189

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 189

cccaucugcu aggauuguu

19

<210> SEQ ID NO 190

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 190

aacaauccua gcagauggg

19

<210> SEQ ID NO 191

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 191

cugcuaggau uguugucgu

19

<210> SEQ ID NO 192

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 192

acgacaacaa uccuagcag 19

<210> SEQ ID NO 193

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 193

ggauuguugu cguuacuau 19

<210> SEQ ID NO 194

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 194

auaguaacga caacaaucc 19

<210> SEQ ID NO 195

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 195

gauuguuguc guuacuaua 19

<210> SEQ ID NO 196

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 196

uauaguaacg acaacaaucc 19

<210> SEQ ID NO 197

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 197

uucuuuuuuu uaucgagca 19

<210> SEQ ID NO 198

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 198

ugcucgauaa aaauaagaa 19

<210> SEQ ID NO 199

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 199

uaauuuuaua gagcacaaa 19

<210> SEQ ID NO 200

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 200

uuugugcucg auaaaaaaua 19

<210> SEQ ID NO 201

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 201

uuuauaagag acaaacgga 19

<210> SEQ ID NO 202

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 202

uccguuugug cugauaaa 19

<210> SEQ ID NO 203

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 203

auggcagccu cugcuuaga 19

<210> SEQ ID NO 204

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 204

ucuaagcaga ggcugccau

19

&lt;210&gt; SEQ ID NO 205

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 205

gcagccucug cuuagaaaa

19

&lt;210&gt; SEQ ID NO 206

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 206

uuuucuaagc agaggcugc

19

&lt;210&gt; SEQ ID NO 207

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 207

cagccucugc uuagaaaaa

19

&lt;210&gt; SEQ ID NO 208

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 208

uuuuucuaag cagaggcug

19

&lt;210&gt; SEQ ID NO 209

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 209

acgccagagg augacgauu

19

&lt;210&gt; SEQ ID NO 210

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 210

aaucgucauc cucuggcgu

19

&lt;210&gt; SEQ ID NO 211

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 211

gccagaggau gacgauugu

19

&lt;210&gt; SEQ ID NO 212

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 212

acaaucguca uccucuggc

19

&lt;210&gt; SEQ ID NO 213

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 213

ccagaggau acgauuguu

19

&lt;210&gt; SEQ ID NO 214

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 214

aacaaucguc auccucugg

19

&lt;210&gt; SEQ ID NO 215

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 215

cagaggaua cgauuguuu

19

&lt;210&gt; SEQ ID NO 216

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 216

aaacaaucgu cauccucug

19

<210> SEQ ID NO 217

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 217

agaggaugac gauuguuua

19

<210> SEQ ID NO 218

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 218

uaaacaauug ucauccucu

19

<210> SEQ ID NO 219

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 219

gaggaugacg auuguuuau

19

<210> SEQ ID NO 220

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 220

auaaacaau gucauccuc

19

<210> SEQ ID NO 221

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 221

ggaugacgau uguuuauca

19

<210> SEQ ID NO 222

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 222

ugauaaacaa ucgucaucc

19

&lt;210&gt; SEQ ID NO 223

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 223

gacgauuguu uaucaacgu

19

&lt;210&gt; SEQ ID NO 224

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 224

acguugauaa acaaucguc

19

&lt;210&gt; SEQ ID NO 225

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 225

cgauuguuuu ucaacguca

19

&lt;210&gt; SEQ ID NO 226

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 226

ugacguugau aaacaaucg

19

&lt;210&gt; SEQ ID NO 227

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 227

gauuguuuau caacgucau

19

&lt;210&gt; SEQ ID NO 228

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 228

augacguuga uaaacaauC

19

&lt;210&gt; SEQ ID NO 229

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 229

uuguuuauca acgucaucU

19

&lt;210&gt; SEQ ID NO 230

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 230

agaugacguu gauaaacaa

19

&lt;210&gt; SEQ ID NO 231

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 231

uguuuuaucaa cgucaucua

19

&lt;210&gt; SEQ ID NO 232

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 232

uagaugacgu ugauaaaca

19

&lt;210&gt; SEQ ID NO 233

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 233

uuuaucaacg ucaucuaga

19

&lt;210&gt; SEQ ID NO 234

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 234

ucuagaugac guugauaaa

19

<210> SEQ ID NO 235

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 235

aucaacguca ucuagagga

19

<210> SEQ ID NO 236

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 236

uccucuagau gacguugau

19

<210> SEQ ID NO 237

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 237

ucaacgucau cuagaggaa

19

<210> SEQ ID NO 238

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 238

uuccucuaga ugacguuga

19

<210> SEQ ID NO 239

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 239

acgucaucua gaggaauuu

19

<210> SEQ ID NO 240

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 240  
aaaauccucu agaagacgu 19

<210> SEQ ID NO 241  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 241  
caaacaggaa cacauagca 19

<210> SEQ ID NO 242  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 242  
ugcuaugugu uccuguuug 19

<210> SEQ ID NO 243  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 243  
caggaacaca uagcagaua 19

<210> SEQ ID NO 244  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 244  
uaucugcuau guguuccug 19

<210> SEQ ID NO 245  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 245  
aggaacacau agcagauaa 19

<210> SEQ ID NO 246  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 246

uuaucugcua uguguuccu

19

&lt;210&gt; SEQ ID NO 247

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 247

ggaacacaua gcagauaaa

19

&lt;210&gt; SEQ ID NO 248

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 248

uuuauucugcu auguguucc

19

&lt;210&gt; SEQ ID NO 249

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 249

acauagcaga uaaacuucu

19

&lt;210&gt; SEQ ID NO 250

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 250

agaaguuuau cugcuau

19

&lt;210&gt; SEQ ID NO 251

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 251

ugccccgcag gguuuugu

19

&lt;210&gt; SEQ ID NO 252

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 252

acaaaauccc ugcggggca

19

&lt;210&gt; SEQ ID NO 253

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 253

gccccgcagg guuuugua

19

&lt;210&gt; SEQ ID NO 254

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 254

uacaaaauacc cugcggggc

19

&lt;210&gt; SEQ ID NO 255

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 255

ccccgcaggg uuuuuguaa

19

&lt;210&gt; SEQ ID NO 256

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 256

uuacaaaauac ccugcgggg

19

&lt;210&gt; SEQ ID NO 257

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 257

cccgcagggg auuuguaaa

19

&lt;210&gt; SEQ ID NO 258

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 258

uuuacaaaaua ccucugcggg

19

<210> SEQ ID NO 259

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 259

cgcagggauu uuguuaaga

19

<210> SEQ ID NO 260

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 260

ucuuuacaaa uaccucgcg

19

<210> SEQ ID NO 261

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 261

gcccagcagc uacacaugu

19

<210> SEQ ID NO 262

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 262

acauguguag cugcugggc

19

<210> SEQ ID NO 263

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 263

cccagcagcu acacaugua

19

<210> SEQ ID NO 264

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 264

uacaugugua gcugcuggg

19

&lt;210&gt; SEQ ID NO 265

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 265

agcuacacau guacaacuu

19

&lt;210&gt; SEQ ID NO 266

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 266

aaguuguaca uguguagcu

19

&lt;210&gt; SEQ ID NO 267

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 267

uacacaugua caacuugca

19

&lt;210&gt; SEQ ID NO 268

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 268

ugcaaguugu acaugugua

19

&lt;210&gt; SEQ ID NO 269

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 269

acacauguac aacuugcaa

19

&lt;210&gt; SEQ ID NO 270

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 270

uugcaaguug uacaugugu

19

&lt;210&gt; SEQ ID NO 271

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 271

uacaacuugc aaacagcca

19

&lt;210&gt; SEQ ID NO 272

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 272

uggcuguuug caaguugua

19

&lt;210&gt; SEQ ID NO 273

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 273

aacacgcaca gaacacuca

19

&lt;210&gt; SEQ ID NO 274

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 274

ugaguguucu gugcguguu

19

&lt;210&gt; SEQ ID NO 275

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 275

gcacagaaca cucauggau

19

&lt;210&gt; SEQ ID NO 276

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 276

auccaugagu guucugugc

19

&lt;210&gt; SEQ ID NO 277

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 277

cacagaacac ucauggauu

19

&lt;210&gt; SEQ ID NO 278

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 278

aauccaugag uguucugug

19

&lt;210&gt; SEQ ID NO 279

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 279

cagaacacuc auggauuaa

19

&lt;210&gt; SEQ ID NO 280

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 280

uuauccaug aguguucug

19

&lt;210&gt; SEQ ID NO 281

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 281

gaacacucau ggauuaaga

19

&lt;210&gt; SEQ ID NO 282

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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&lt;400&gt; SEQUENCE: 282

ucuaaaucca ugaguguuc

19

&lt;210&gt; SEQ ID NO 283

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 283

aacacucaug gauuaagaa

19

&lt;210&gt; SEQ ID NO 284

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 284

uucuaaucc augaguguu

19

&lt;210&gt; SEQ ID NO 285

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 285

acacucaugg auuaagaau

19

&lt;210&gt; SEQ ID NO 286

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 286

auucuaauac caugagugu

19

&lt;210&gt; SEQ ID NO 287

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 287

acucauggau uaagaau

19

&lt;210&gt; SEQ ID NO 288

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 288

agauucuuuaa uccaugagu

19

&lt;210&gt; SEQ ID NO 289

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 289

gauuaagaau cuacuuaga

19

&lt;210&gt; SEQ ID NO 290

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 290

ucuaaguaga uucuuauuc

19

&lt;210&gt; SEQ ID NO 291

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 291

auuaagaauuc uacuuagaa

19

&lt;210&gt; SEQ ID NO 292

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 292

uucuaaguag auucuuauu

19

&lt;210&gt; SEQ ID NO 293

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 293

uuuaucgagc acaaacggat t

21

&lt;210&gt; SEQ ID NO 294

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 294

uccguuugug cucgauaaat t                                     21

<210> SEQ ID NO 295
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 295

auggcagccu cugcuuagat t                                     21

<210> SEQ ID NO 296
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 296

ucuaagcaga ggcugccaut t                                     21

<210> SEQ ID NO 297
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 297

gcagccucug cuuagaaaat t                                     21

<210> SEQ ID NO 298
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 298

uuuucuaagc agaggcugct t                                     21

<210> SEQ ID NO 299
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 299

cagccucugc uuagaaaaat t                               21

<210> SEQ ID NO 300
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 300

uuuuucuaag cagaggcugt t                               21

<210> SEQ ID NO 301
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 301

acgccagagg augacgau t                                 21

<210> SEQ ID NO 302
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 302

aaucgucauc cucuggcgut t                               21

<210> SEQ ID NO 303
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 303

gccagaggau gacgauugt t                               21

<210> SEQ ID NO 304
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 304

acaaucguca uccucuggt t 21

<210> SEQ ID NO 305  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 305

ccagaggau g acgauugu t 21

<210> SEQ ID NO 306  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 306

aacaaucguc auccucugt t 21

<210> SEQ ID NO 307  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 307

cagaggau g cgauuguu t 21

<210> SEQ ID NO 308  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 308

aaacaaucg ucauccucgt t 21

<210> SEQ ID NO 309  
<211> LENGTH: 21  
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 309

agaggaugac gauuguuuat t 21

<210> SEQ ID NO 310
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 310

uaaacaauug ucauccucut t 21

<210> SEQ ID NO 311
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 311

gaggaugacg auuguuuaut t 21

<210> SEQ ID NO 312
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 312

auaaacaauuc gucauccut t 21

<210> SEQ ID NO 313
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 313

ggaugacgau uguuuaucau t 21

<210> SEQ ID NO 314
<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 314

ugauaaacaa ucgucaucct t                                     21

<210> SEQ ID NO 315
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 315

gacgauuguu uaucaacgut t                                     21

<210> SEQ ID NO 316
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 316

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cgauuguuuu ucaacgucac t                                     21

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<400> SEQUENCE: 323

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<400> SEQUENCE: 333

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<400> SEQUENCE: 334

uauucgcuau guguuuccgt t                                     21

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<400> SEQUENCE: 335

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 376

auucuuauuc caugagugut t

21

<210> SEQ ID NO 377

<211> LENGTH: 21

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:

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 Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 377

acucauggau uaagaau cut t 21

&lt;210&gt; SEQ ID NO 378

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 378

agauucuuuaa uccaugagut t 21

&lt;210&gt; SEQ ID NO 379

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 379

gauuaagaau cuacuuagat t 21

&lt;210&gt; SEQ ID NO 380

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 380

ucuaaguaga uucuuauauct t 21

&lt;210&gt; SEQ ID NO 381

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 381

ugguaucccu ucaggacua 19

&lt;210&gt; SEQ ID NO 382

&lt;211&gt; LENGTH: 19

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 382

uaguccugaa gggauacca 19

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<210> SEQ ID NO 383  
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 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <400> SEQUENCE: 383  
  
 cuaggugcag aauguccuu 19

<210> SEQ ID NO 384  
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 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 aaggacauuc ugcaccuag 19

<210> SEQ ID NO 385  
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 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
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 gccaccucuc caugggauu 19

<210> SEQ ID NO 386  
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 <212> TYPE: RNA  
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 <400> SEQUENCE: 386  
  
 aaucCCAUGG agagguggc 19

<210> SEQ ID NO 387  
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 ugcagacaau aacCCCUUU 19

<210> SEQ ID NO 388  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <400> SEQUENCE: 388  
  
 aaagggguua uugucugca 19

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<210> SEQ ID NO 389  
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<212> TYPE: RNA  
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 389

acaauaaccc cuuuaaccu 19

<210> SEQ ID NO 390  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 390

agguuaaagg gguuauugu 19

<210> SEQ ID NO 391  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 391

ccccuuuac cugcuaaga 19

<210> SEQ ID NO 392  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 392

ucuuagcagg uuaaagggg 19

<210> SEQ ID NO 393  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
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oligonucleotide

<400> SEQUENCE: 393

ccuuuaaccu gcuaagaau 19

<210> SEQ ID NO 394  
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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 394

auucuuagca gguuaaagg 19

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<210> SEQ ID NO 395  
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 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <210> SEQ ID NO 396  
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 <212> TYPE: RNA  
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <400> SEQUENCE: 396  
  
 auacugaucc ugguauucu 19  
  
 <210> SEQ ID NO 397  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <400> SEQUENCE: 397  
  
 auaccaggau caguaucga 19  
  
 <210> SEQ ID NO 398  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
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 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 ucgauacuga uccugguau 19  
  
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 <212> TYPE: RNA  
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 <220> FEATURE:  
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 <400> SEQUENCE: 399  
  
 accaggauca guaucgaga 19  
  
 <210> SEQ ID NO 400  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
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 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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 <400> SEQUENCE: 400  
  
 ucucgauacu gaucuggu 19  
  
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<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 401

caccaccgag acaucacuu 19

<210> SEQ ID NO 402  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 402

aagugauguc ucgguggug 19

<210> SEQ ID NO 403  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 403

cagggugcug cgguugaau 19

<210> SEQ ID NO 404  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 404

auucaaccgc agcaccug 19

<210> SEQ ID NO 405  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 405

cgguugaau caauggcua 19

<210> SEQ ID NO 406  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 406

uagccauugg auucaaccg 19

<210> SEQ ID NO 407  
<211> LENGTH: 19

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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 407

gagccucccg ccauggauu 19

<210> SEQ ID NO 408  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 408

aauccauggc gggaggcuc 19

<210> SEQ ID NO 409  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 409

agccuccgc cauggauuu 19

<210> SEQ ID NO 410  
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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 410

aaauccaugg cgggaggcu 19

<210> SEQ ID NO 411  
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<212> TYPE: RNA  
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 411

ggauuucucu aggagacuu 19

<210> SEQ ID NO 412  
<211> LENGTH: 19  
<212> TYPE: RNA  
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 412

aagucuccua gagaaaucc 19

<210> SEQ ID NO 413  
<211> LENGTH: 19  
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 413

ccagcccuau gcaaagguu 19

<210> SEQ ID NO 414  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
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oligonucleotide

<400> SEQUENCE: 414

aaccuuugca uagggcugg 19

<210> SEQ ID NO 415  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 415

aaagguuacu gcaaccauu 19

<210> SEQ ID NO 416  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 416

aaugguugca gaaacuuu 19

<210> SEQ ID NO 417  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 417

aguccaaguc augcgaguu 19

<210> SEQ ID NO 418  
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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 418

aacucgcaug acuuggacu 19

<210> SEQ ID NO 419  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
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<400> SEQUENCE: 419

cgccaccacg agaacagcu                               19

<210> SEQ ID NO 420
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 420

agcuguucuc guggugcg                               19

<210> SEQ ID NO 421
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 421

guccugggcg agaagcaua                               19

<210> SEQ ID NO 422
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 422

uaugcuucuc gcccaggac                               19

<210> SEQ ID NO 423
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 423

uccugggcga gaagcauaa                               19

<210> SEQ ID NO 424
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 424

uuauuguucu cgcccagga                               19

<210> SEQ ID NO 425
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 425

gacacuugcg acgaagacu 19

<210> SEQ ID NO 426  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 426

agucuucguc gcaaguguc 19

<210> SEQ ID NO 427  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 427

agucggaccg cauagacga 19

<210> SEQ ID NO 428  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 428

ucgucuauhc gguccgacu 19

<210> SEQ ID NO 429  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 429

gucggaccgc auagacgau 19

<210> SEQ ID NO 430  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 430

aucgucuauhc cgguccgac 19

<210> SEQ ID NO 431  
<211> LENGTH: 19  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 431

cgcgagagccc cuucucuaa 19

<210> SEQ ID NO 432  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 432

uuagagaagg ggcucagcg 19

<210> SEQ ID NO 433  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 433

gccccuucuc uaagcgcau 19

<210> SEQ ID NO 434  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 434

augcgcuuag agaaggggc 19

<210> SEQ ID NO 435  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 435

cuccaggcag cucaaagau 19

<210> SEQ ID NO 436  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 436

aucuuugagc ugccuggag 19

<210> SEQ ID NO 437  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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<400> SEQUENCE: 437

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19

<210> SEQ ID NO 438

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 438

agggaucuuu gagcugccu

19

<210> SEQ ID NO 439

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 439

ggcagcucaa agaucuuu

19

<210> SEQ ID NO 440

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 440

aagggaucuu ugagcugcc

19

<210> SEQ ID NO 441

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 441

cucaaagauc ccuuccuua

19

<210> SEQ ID NO 442

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 442

uaaggaaggg aucuuugag

19

<210> SEQ ID NO 443

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 443

acuccagaca aucgccuuu

19

<210> SEQ ID NO 444

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 444

aaaggcgauu gucuggagu

19

<210> SEQ ID NO 445

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 445

agggagcacg ccccauauu

19

<210> SEQ ID NO 446

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 446

aaauaggggc gugcuccu

19

<210> SEQ ID NO 447

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 447

gggagcacgc cccauauua

19

<210> SEQ ID NO 448

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 448

uaauaugggg cgugcuccc

19

<210> SEQ ID NO 449

<211> LENGTH: 19

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 449

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gagcacgccc cauauuagu 19

<210> SEQ ID NO 450  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 450

acuaauaugg ggcgugcuc 19

<210> SEQ ID NO 451  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 451

cacgccccau auuaguggu 19

<210> SEQ ID NO 452  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 452

accacuaaua uggggugug 19

<210> SEQ ID NO 453  
 <211> LENGTH: 21  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
 Synthetic oligonucleotide

<400> SEQUENCE: 453

ugguaucccu ucaggacuat t 21

<210> SEQ ID NO 454  
 <211> LENGTH: 21  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 512

aagggaucuu ugacugcct t 21

&lt;210&gt; SEQ ID NO 513

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 513

cucaaagauc ccuuccuat t 21

&lt;210&gt; SEQ ID NO 514

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<400> SEQUENCE: 514

uaaggaaggg aucuuugagt t 21

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oligonucleotide  
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aaagcggaau gucuggagut t 21

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
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<400> SEQUENCE: 517

agggagcacg ccccauauut t 21

<210> SEQ ID NO 518  
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<400> SEQUENCE: 518

aaauaggggc gugucccut t 21

<210> SEQ ID NO 519  
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<220> FEATURE:
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<400> SEQUENCE: 519

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<210> SEQ ID NO 520
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uaauaugggg cgugcuccct t                                     21

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<210> SEQ ID NO 522
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<220> FEATURE:
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<400> SEQUENCE: 522

acuaauaugg ggcgugcuct t                                     21

<210> SEQ ID NO 523
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 523

cacgcccgau auuaguggut t                                     21

<210> SEQ ID NO 524
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 524

accacuaaaua uggggcgugt t                                     21

<210> SEQ ID NO 525
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<400> SEQUENCE: 525

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<210> SEQ ID NO 526
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<400> SEQUENCE: 526

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<400> SEQUENCE: 527

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 528

aaacugucgu gcaaaccat t                                     21

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<400> SEQUENCE: 529

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aagcgaggcc gacguucgut t 21

<210> SEQ ID NO 531  
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acgaacgucg gccucgcuut t 21

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<212> TYPE: DNA  
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aaauaacgga cucaguggat t 21

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<400> SEQUENCE: 533  
  
uccacugagu ccguuuauut t 21

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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aaugguuaug gguccuauat t 21

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uauaggaccc auaaccaut t 21

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uuuauuuggc ggucugucut t 21

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uccguuuuuu uggeggucut t 21

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<400> SEQUENCE: 546

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

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<400> SEQUENCE: 549

auauuugggu ggaucuuugt t

21

<210> SEQ ID NO 550

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<212> TYPE: DNA

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<220> FEATURE:

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<220> FEATURE:

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<400> SEQUENCE: 550

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<210> SEQ ID NO 551

<211> LENGTH: 21

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<220> FEATURE:

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<220> FEATURE:

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<400> SEQUENCE: 551

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<400> SEQUENCE: 552

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<220> FEATURE:

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<400> SEQUENCE: 553

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21

<210> SEQ ID NO 554

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<220> FEATURE:

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<220> FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:

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Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 554

ccuccuuccu gaguuguuut t 21

&lt;210&gt; SEQ ID NO 555

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

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&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 555

aaacaacuca ggaaggaggt t 21

&lt;210&gt; SEQ ID NO 556

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 556

ccugaagguc ccuuauugut t 21

&lt;210&gt; SEQ ID NO 557

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 557

acaauaaggg accuucaggt t 21

&lt;210&gt; SEQ ID NO 558

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Combined DNA/RNA Molecule: Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 558

ccuuauugug gcugauauut t 21

&lt;210&gt; SEQ ID NO 559

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

&lt;220&gt; FEATURE:

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<400> SEQUENCE: 559

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<210> SEQ ID NO 560  
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Synthetic oligonucleotide

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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 561

aaauaucagcc acaauaaggt t 21

<210> SEQ ID NO 562  
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<400> SEQUENCE: 562

cgagacucug ggcgcuaaut t 21

<210> SEQ ID NO 563  
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Synthetic oligonucleotide

<400> SEQUENCE: 563

auaugcgccc agagucucgt t 21

<210> SEQ ID NO 564  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 564

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<210> SEQ ID NO 565
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 565

ugaguccguu uauuuggcgt t                                     21

<210> SEQ ID NO 566
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 566

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<210> SEQ ID NO 567
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 567

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<210> SEQ ID NO 568
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<220> FEATURE:
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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cuccugaagg ucccuauut t                                     21

<210> SEQ ID NO 569
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 569

aauaaggac cuucaggagt t                21

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<400> SEQUENCE: 570

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<220> FEATURE:
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    Synthetic oligonucleotide

<400> SEQUENCE: 571

uuugggaacg cgaguccagt t                21

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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    oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 572

cugggucuag aaagcggcut t                21

<210> SEQ ID NO 573
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
    Synthetic oligonucleotide

<400> SEQUENCE: 573

agccgcuuuc uagacccagt t                21

<210> SEQ ID NO 574
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 574

cuuacggaaa auccgacaat t                               21

<210> SEQ ID NO 575
<211> LENGTH: 21
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oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 575

uugucggauu uuccgaaagt t                               21

<210> SEQ ID NO 576
<211> LENGTH: 21
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 576

gacucagugg acacucagat t                               21

<210> SEQ ID NO 577
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 577

ucugaguguc cacugaguct t                               21

<210> SEQ ID NO 578
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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oligonucleotide
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 578

gagacagacc gccaaauaat t                               21

<210> SEQ ID NO 579
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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Synthetic oligonucleotide  
  
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uuauuuggcg gucugucuct t 21  
  
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Synthetic oligonucleotide  
  
<400> SEQUENCE: 580  
  
gagaugucca aacugucgut t 21  
  
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<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide  
  
<400> SEQUENCE: 581  
  
acgacaguuu ggacaucuct t 21  
  
<210> SEQ ID NO 582  
<211> LENGTH: 21  
<212> TYPE: DNA  
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
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Synthetic oligonucleotide  
  
<400> SEQUENCE: 582  
  
gccccuccac gugaagucut t 21  
  
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<211> LENGTH: 21  
<212> TYPE: DNA  
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide  
  
<400> SEQUENCE: 583  
  
agacuucacg uggaggggct t 21  
  
<210> SEQ ID NO 584  
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
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Synthetic oligonucleotide

<400> SEQUENCE: 584

gcccgggcac uggacucut t                                     21

<210> SEQ ID NO 585
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 585

agaguccaag ugccagggt t                                     21

<210> SEQ ID NO 586
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oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 586

gcuccugaag guccuuaut t                                     21

<210> SEQ ID NO 587
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<212> TYPE: DNA
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oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 587

auaagggacc uucaggagct t                                     21

<210> SEQ ID NO 588
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 588

ggaaaaucgg acaagccuut t                                     21

<210> SEQ ID NO 589
<211> LENGTH: 21

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<212> TYPE: DNA  
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide  
  
<400> SEQUENCE: 589  
  
aaggcuuguc ggauuuucct t 21  
  
<210> SEQ ID NO 590  
<211> LENGTH: 21  
<212> TYPE: DNA  
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oligonucleotide  
<220> FEATURE:  
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Synthetic oligonucleotide  
  
<400> SEQUENCE: 590  
  
guccaaacug ucgugcaa t 21  
  
<210> SEQ ID NO 591  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
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oligonucleotide  
<220> FEATURE:  
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Synthetic oligonucleotide  
  
<400> SEQUENCE: 591  
  
uuugcacgac aguuuggact t 21  
  
<210> SEQ ID NO 592  
<211> LENGTH: 21  
<212> TYPE: DNA  
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oligonucleotide  
<220> FEATURE:  
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gugcaaacc agugagacat t 21  
  
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<211> LENGTH: 21  
<212> TYPE: DNA  
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<400> SEQUENCE: 593  
  
ugucucacug gguuugcact t 21  
  
<210> SEQ ID NO 594

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<211> LENGTH: 21
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<220> FEATURE:
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 594

uaucaaacac ggacccauat t                               21

<210> SEQ ID NO 595
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 595

uaugggucgc uguuugauat t                               21

<210> SEQ ID NO 596
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 596

ucccuauug uggcugauat t                               21

<210> SEQ ID NO 597
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 597

uaucaagccac aaauagggat t                               21

<210> SEQ ID NO 598
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 598

ucccuauug uggcugauau u                               21

<210> SEQ ID NO 599
<211> LENGTH: 23
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 599

aaauaucagcc acaauaaggg acc                23

<210> SEQ ID NO 600
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 600

ucuccuagug acuggggaut t                    21

<210> SEQ ID NO 601
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 601

auccccaguc acuaggagat t                    21

<210> SEQ ID NO 602
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 602

ucuuacggaa aauccgacat t                    21

<210> SEQ ID NO 603
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 603

ugucggauuu uccguaagat t                    21

<210> SEQ ID NO 604
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 604

ugagacagac cgccaaauat t                               21

<210> SEQ ID NO 605
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 605

uauuuggcgg ucugucuat t                               21

<210> SEQ ID NO 606
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 606

uggcacuugg acucuccuat t                               21

<210> SEQ ID NO 607
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 607

uaggagaguc caagugccat t                               21

<210> SEQ ID NO 608
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 608

uggcgcugca accgguguat t                               21

<210> SEQ ID NO 609
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:  
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oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 609

uacaccgguu gcagcgccat t 21

<210> SEQ ID NO 610  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
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<400> SEQUENCE: 610

ugguuauggg uccuauaaat t 21

<210> SEQ ID NO 611  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 611

uuuauaggac ccauaaccat t 21

<210> SEQ ID NO 612  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 612

ugguuuuccc acgauggat t 21

<210> SEQ ID NO 613  
<211> LENGTH: 21  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

<400> SEQUENCE: 613

uccauucgug ggaaaaccat t 21

<210> SEQ ID NO 614  
<211> LENGTH: 21  
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 614

uguccaaacu gucgugcaat t                               21

<210> SEQ ID NO 615
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 615

uugcacgaca guuuggacat t                               21

<210> SEQ ID NO 616
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 616

uguggcugau auuaacugut t                               21

<210> SEQ ID NO 617
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 617

acaguuaaau ucagccacat t                               21

<210> SEQ ID NO 618
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
Synthetic oligonucleotide

<400> SEQUENCE: 618

uuucccacga auggaccut t                               21

<210> SEQ ID NO 619
<211> LENGTH: 21

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 619

aggguccauu cgugggaaat t                               21

<210> SEQ ID NO 620
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 620

uuuuggguuc ggaggauca t                               21

<210> SEQ ID NO 621
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
        Synthetic oligonucleotide

<400> SEQUENCE: 621

ugauccuccg aacccaaaat t                               21

<210> SEQ ID NO 622
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 622

Glu Tyr Cys Gly Lys Val Phe Lys Asn Cys Ser Asn Leu Thr Val His
1      5      10      15
Arg Arg Ser His Thr Gly Glu Arg Pro Tyr Lys Cys Glu
      20      25

<210> SEQ ID NO 623
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        peptide

<400> SEQUENCE: 623

Ser Ser His Thr Pro Ile Arg Arg Ser Thr Gln Arg Ala Gln Asp Val
1      5      10      15
Trp Gln Phe Ser Asp Gly Ser Ser Arg Ala Leu Lys Phe
      20      25

<210> SEQ ID NO 624
<211> LENGTH: 32

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<212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 624

Gly Ile Pro Ser Gly Leu Gly Ala Glu Cys Pro Ser Gln Pro Pro Leu  
 1                   5                   10                   15  
 His Gly Ile His Ile Ala Asp Asn Asn Pro Phe Asn Leu Leu Arg Ile  
           20                   25                   30

<210> SEQ ID NO 625  
 <211> LENGTH: 32  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
                                   polypeptide

<400> SEQUENCE: 625

Leu His Thr Pro Pro Phe Gly Val Val Pro Arg Glu Leu Lys Met Cys  
 1                   5                   10                   15  
 Gly Ser Phe Arg Met Glu Ala Arg Glu Pro Leu Ser Ser Glu Lys Ile  
           20                   25                   30

<210> SEQ ID NO 626  
 <211> LENGTH: 21  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
                                   oligonucleotide  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
                                   Synthetic oligonucleotide

<400> SEQUENCE: 626

uuuau cgagc acaaacggat t 21

<210> SEQ ID NO 627  
 <211> LENGTH: 21  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
                                   oligonucleotide  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
                                   Synthetic oligonucleotide

<400> SEQUENCE: 627

uccguuugug cucgauaaat t 21

<210> SEQ ID NO 628  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
                                   oligonucleotide

<400> SEQUENCE: 628

uuuuuau cga gcacaaacgg a 21

<210> SEQ ID NO 629  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 629

uccguuugug cucgauaaaa aua                                     23

<210> SEQ ID NO 630
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 630

uuuuuauucga gcacaaacgg a                                     21

<210> SEQ ID NO 631
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 631

uccguuugug cucgauaaaa aua                                     23

<210> SEQ ID NO 632
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 632

uuuuuauucga gcacaaacgg a                                     21

<210> SEQ ID NO 633
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 633

uccguuugug cucgauaaaa aua                                     23

<210> SEQ ID NO 634
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 634

uuuuuauucga gcacaaacgg a                                     21

<210> SEQ ID NO 635
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 635

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 636  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 636

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 637  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 637

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 638  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 638

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 639  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 639

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 640  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 640

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 641  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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<400> SEQUENCE: 641

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 642

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 642

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 643

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 643

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 644

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 644

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 645

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 645

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 646

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 646

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 647

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 647

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 648

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 648

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 649

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 649

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 650

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 650

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 651

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 651

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 652

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 652

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 653

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 653

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uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 654  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 654

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 655  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 655

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 656  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 656

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 657  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 657

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 658  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 658

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 659  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 659

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uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 660  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 660

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 661  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 661

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 662  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 662

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 663  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 663

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 664  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 664

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 665  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 665

uccguuugug cucgauaaaa aua 23

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<210> SEQ ID NO 666  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 666  
 uuuaucgagc acaaacgga 19

<210> SEQ ID NO 667  
 <211> LENGTH: 19  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 667  
 uccguuugug cucgauaaa 19

<210> SEQ ID NO 668  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 668  
 uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 669  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 669  
 uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 670  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 670  
 uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 671  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide  
  
 <400> SEQUENCE: 671  
 uccguuugug cucgauaaaa aua 23

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<210> SEQ ID NO 672
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 672

uuuuuauucga gcacaaacgg a                               21

<210> SEQ ID NO 673
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 673

uccguuugug cucgauaaaa aua                               23

<210> SEQ ID NO 674
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 674

uuuuuauucga gcacaaacgg a                               21

<210> SEQ ID NO 675
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 675

uccguuugug cucgauaaaa aua                               23

<210> SEQ ID NO 676
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 676

uuuuuauucga gcacaaacgg a                               21

<210> SEQ ID NO 677
<400> SEQUENCE: 677

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<210> SEQ ID NO 678
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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oligonucleotide

<400> SEQUENCE: 678

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 679  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 679

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 680  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 680

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 681  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 681

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 682  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 682

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 683  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 683

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 684  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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&lt;400&gt; SEQUENCE: 684

uccguuugug cucgauaaaa aua 23

&lt;210&gt; SEQ ID NO 685

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 685

uuuuuauca gcacaaacgg a 21

&lt;210&gt; SEQ ID NO 686

&lt;211&gt; LENGTH: 23

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 686

uccguuugug cucgauaaaa aua 23

&lt;210&gt; SEQ ID NO 687

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 687

uuuuuauca gcacaaacgg a 21

&lt;210&gt; SEQ ID NO 688

&lt;211&gt; LENGTH: 23

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 688

uccguuugug cucgauaaaa aua 23

&lt;210&gt; SEQ ID NO 689

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 689

uuuuuauca gcacaaacgg a 21

&lt;210&gt; SEQ ID NO 690

&lt;211&gt; LENGTH: 23

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

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<400> SEQUENCE: 690

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 691

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 691

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 692

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 692

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 693

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 693

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 694

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 694

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 695

<211> LENGTH: 21

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 695

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 696

<211> LENGTH: 23

<212> TYPE: RNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 696

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uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 697  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 697

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 698  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 698

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 699  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 699

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 700  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 700

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 701  
<211> LENGTH: 21  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 701

uuuuuauca gcacaaacgg a 21

<210> SEQ ID NO 702  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 702

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uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 703  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 703

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 704  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 704

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 705  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 705

uuuuuauucga gcacaaacgg a 21

<210> SEQ ID NO 706  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 706

uccguuugug cucgauaaaa aua 23

<210> SEQ ID NO 707  
 <211> LENGTH: 16  
 <212> TYPE: PRT  
 <213> ORGANISM: Unknown  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Unknown: Exemplary hydrophobic  
 membrane translocations sequence peptide

<400> SEQUENCE: 707

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro  
 1 5 10 15

<210> SEQ ID NO 708  
 <211> LENGTH: 11  
 <212> TYPE: PRT  
 <213> ORGANISM: Unknown  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Unknown: RFGF analogue peptide

<400> SEQUENCE: 708

Ala Ala Leu Leu Pro Val Leu Leu Ala Ala Pro

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1                      5                      10

<210> SEQ ID NO 709  
 <211> LENGTH: 13  
 <212> TYPE: PRT  
 <213> ORGANISM: Human immunodeficiency virus

<400> SEQUENCE: 709

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln  
 1                      5                      10

<210> SEQ ID NO 710  
 <211> LENGTH: 16  
 <212> TYPE: PRT  
 <213> ORGANISM: Drosophila sp.

<400> SEQUENCE: 710

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys  
 1                      5                      10                      15

<210> SEQ ID NO 711  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 711

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 712  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 712

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 713  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 713

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 714  
 <211> LENGTH: 23  
 <212> TYPE: RNA  
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 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
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<400> SEQUENCE: 714

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<210> SEQ ID NO 715  
 <211> LENGTH: 21

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<212> TYPE: RNA  
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 715

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 716  
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oligonucleotide

<400> SEQUENCE: 716

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<210> SEQ ID NO 717  
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<212> TYPE: RNA  
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<400> SEQUENCE: 717

ucccuuauug uggcugauau u 21

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oligonucleotide

<400> SEQUENCE: 718

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<400> SEQUENCE: 719

ucccuuauug uggcugauau u 21

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oligonucleotide

<400> SEQUENCE: 720

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<210> SEQ ID NO 721  
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        oligonucleotide

<400> SEQUENCE: 721

ucccuuauug uggcugauau u                                21

<210> SEQ ID NO 722
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<400> SEQUENCE: 722

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<400> SEQUENCE: 724

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<211> LENGTH: 21
<212> TYPE: RNA
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<220> FEATURE:
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        oligonucleotide

<400> SEQUENCE: 725

ucccuuauug uggcugauau u                                21

<210> SEQ ID NO 726
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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        oligonucleotide

<400> SEQUENCE: 726

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<210> SEQ ID NO 727
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
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<400> SEQUENCE: 727

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<210> SEQ ID NO 728
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 728

aaauaucagcc acaauaaggg acc                                   23

<210> SEQ ID NO 729
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 729

ucccuuauug uggcugauau u                                     21

<210> SEQ ID NO 730
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

<400> SEQUENCE: 730

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<210> SEQ ID NO 731
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<212> TYPE: RNA
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<400> SEQUENCE: 731

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<210> SEQ ID NO 732
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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 732

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<210> SEQ ID NO 733
<211> LENGTH: 21
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<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 733

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 734  
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<212> TYPE: RNA  
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<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 734

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<210> SEQ ID NO 735  
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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
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oligonucleotide

<400> SEQUENCE: 735

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 736  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 736

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 737  
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<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

<400> SEQUENCE: 737

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 738  
<211> LENGTH: 23  
<212> TYPE: RNA  
<213> ORGANISM: Artificial Sequence  
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oligonucleotide

<400> SEQUENCE: 738

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 739  
<211> LENGTH: 21  
<212> TYPE: RNA  
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<220> FEATURE:  
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oligonucleotide

<400> SEQUENCE: 739

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 740  
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 <220> FEATURE:  
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<400> SEQUENCE: 740

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 741  
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 oligonucleotide

<400> SEQUENCE: 741

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 742  
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 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
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<400> SEQUENCE: 742

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 743  
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 oligonucleotide

<400> SEQUENCE: 743

ucccuuauug uggcugauau u 21

<210> SEQ ID NO 744  
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 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

<400> SEQUENCE: 744

aaauaucagcc acaauaaggg acc 23

<210> SEQ ID NO 745  
 <211> LENGTH: 21  
 <212> TYPE: RNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
 oligonucleotide

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&lt;400&gt; SEQUENCE: 745

ucccuuauug uggcugauau u 21

&lt;210&gt; SEQ ID NO 746

&lt;211&gt; LENGTH: 23

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 746

aaauaucagcc acaauaaggg acc 23

&lt;210&gt; SEQ ID NO 747

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 747

ucccuuauug uggcugauau u 21

&lt;210&gt; SEQ ID NO 748

&lt;211&gt; LENGTH: 23

&lt;212&gt; TYPE: RNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;400&gt; SEQUENCE: 748

aaauaucagcc acaauaaggg acc 23

&lt;210&gt; SEQ ID NO 749

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 749

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&lt;210&gt; SEQ ID NO 750

&lt;211&gt; LENGTH: 21

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic  
oligonucleotide

&lt;220&gt; FEATURE:

<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:  
Synthetic oligonucleotide

&lt;400&gt; SEQUENCE: 750

aaccgagug auccuccgat t 21

&lt;210&gt; SEQ ID NO 751

&lt;211&gt; LENGTH: 21

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic oligonucleotide

<400> SEQUENCE: 751

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<210> SEQ ID NO 752
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 752

uuugugcugc auaaaaauat t                               21

<210> SEQ ID NO 753
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
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<400> SEQUENCE: 753

cuuuccaggu uccgagucut t                               21

<210> SEQ ID NO 754
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Combined DNA/RNA Molecule:
      Synthetic oligonucleotide

<400> SEQUENCE: 754

agacucggaa ccuggaaagt t                               21

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We claim:

1. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of BCL11A, wherein said dsRNA comprises a sense strand and an antisense strand, wherein said antisense strand comprises a region of complementarity to a BCL11A variant RNA transcript consisting of SEQ ID NO:667 or SEQ ID NO:633, and wherein said dsRNA comprises at least one modified nucleotide.

2. The dsRNA of claim 1, wherein the sense strand consists of the sequence of SEQ ID NO:666 or SEQ ID NO:632.

3. The dsRNA of claim 1, wherein at least one of said modified nucleotide is chosen from: a 2'-O-methyl modified nucleotide, a nucleotide comprising a 5'-phosphorothioate group, or a terminal nucleotide linked to a cholesteryl derivative or dodecanoic acid bisdecylamide group.

4. The dsRNA of claim 1, wherein said modified nucleotide is chosen from: a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, a locked nucleotide, an abasic nucleotide, 2'-amino-modified nucleotide, 2'-alkyl-modified nucleotide, morpholino nucleotide, a phosphoramidate, or a non-natural base comprising nucleotide.

5. The dsRNA of claim 1, wherein the antisense strand has a region of complementarity to a BCL11A variant transcript of at least 17 nucleotides in length.

6. The dsRNA of claim 5, wherein the region of complementarity is between 19 and 21 nucleotides in length.

7. The dsRNA of claim 1, wherein the sense strand is no more than 30 nucleotides in length.

8. The dsRNA of claim 1, wherein at least one strand comprises a 3' overhang of at least 1 or 2 nucleotides.

407

9. The dsRNA of claim 1, further comprising a ligand.
10. The dsRNA of claim 9, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA.
11. The dsRNA of claim 7, wherein the sense strand is between 19 and 24 nucleotides in length.
12. A cell containing the dsRNA of claim 1.
13. A pharmaceutical composition for inhibiting expression of a BCL11A gene comprising the dsRNA of claim 1.
14. The pharmaceutical composition of claim 13, further comprising a lipid formulation.
15. The pharmaceutical composition of claim 14, wherein the lipid formulation is a MC3 formulation.
16. A method of inhibiting BCL11A expression in a cell, the method comprising:
  - (a) introducing into the cell the dsRNA of claim 1; and
  - (b) maintaining the cell produced in step (a) for a time sufficient to obtain degradation of the mRNA transcript of a BCL11A gene, thereby inhibiting expression of the BCL11A gene, or a combination thereof, in the cell.
17. The method of claim 16, wherein the cell is present in a subject in need of treatment, prevention and/or management of a hemoglobinopathy.
18. The method of claim 16, wherein the BCL11A expression is inhibited by at least 30%.
19. The method of claim 16, wherein the dsRNA of claim 1 has an  $IC_{50}$  in the range of 0.001-7 nM.
20. A method of treating a disorder mediated by BCL11A expression comprising administering to a human in need of such treatment a therapeutically effective amount of the dsRNA of claim 1.
21. The method of claim 20, wherein the human is at risk, or is diagnosed with a hemoglobinopathy chosen from a  $\beta$ -hemoglobinopathy, sickle cell disease, or a  $\beta$ -thalassemia.
22. A methods for increasing fetal hemoglobin levels in an erythroid cell, comprising contacting the cell with one or more of the dsRNA of claim 1, in an amount effective to increase fetal hemoglobin levels in the cell, or its progeny.
23. The method of claim 22, wherein the cell is present in a subject at risk of having or having a  $\beta$ -hemoglobin disorders, sickle cell anemia or  $\beta$ -thalassemia.
24. A method for decreasing  $\beta$ -globin levels in an erythroid cell, comprising contacting the cell with one or more of the dsRNA of claim 1, in an amount effective to reduce expres-

408

- sion of BCL11A, thereby decreasing the expression of  $\beta$ -globin in the cell, or its progeny.
25. The method of claim 24, wherein the dsRNA is administered at a concentration of 0.01 mg/kg-5 mg/kg bodyweight of the subject.
26. A vector encoding the dsRNA of claim 1.
27. A cell comprising the vector of claim 26.
28. The dsRNA of claim 1, wherein at least one end of the dsRNA is blunt.
29. The dsRNA of claim 1, wherein the dsRNA comprises a duplex region between 15-30 base pairs.
30. The dsRNA of claim 9, wherein the ligand is a cell or tissue targeting group chosen from a lectin, a glycoprotein, a lipid, or an antibody that binds to a specified cell type.
31. The dsRNA of claim 9, wherein the ligand is a multivalent galactose, N-acetyl-galactosamine, an N-acetyl-galactosamine multivalent mannose, or a cholesterol.
32. A double-stranded ribonucleic acid (dsRNA) for inhibiting expression of BCL11A, wherein said dsRNA comprises a sense strand sequence consisting of SEQ ID NO:626 and an antisense strand sequence consisting of SEQ ID NO:627.
33. The dsRNA of claim 32, further comprising a ligand.
34. The dsRNA of claim 33, wherein the ligand is conjugated to the 3' end of the sense strand of the dsRNA.
35. The dsRNA of claim 33, wherein the ligand is a cell or tissue targeting group chosen from a lectin, a glycoprotein, a lipid, or an antibody that binds to a specified cell type.
36. The dsRNA of claim 33, wherein the ligand is a multivalent galactose, N-acetyl-galactosamine, an N-acetyl-galactosamine multivalent mannose, or a cholesterol.
37. A cell containing the dsRNA of claim 32.
38. A pharmaceutical composition for inhibiting expression of a BCL11A gene comprising the dsRNA of claim 32.
39. The pharmaceutical composition of claim 38, further comprising a lipid formulation.
40. The pharmaceutical composition of claim 39, wherein the lipid formulation is a MC3 formulation.
41. A vector encoding the dsRNA of claim 32.
42. A cell comprising the vector of claim 41.
43. The dsRNA of claim 1, wherein the antisense strand consists of SEQ ID NO:627.
44. The dsRNA of claim 1, wherein the antisense strand consists of SEQ ID NO:639.

\* \* \* \* \*